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BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

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by

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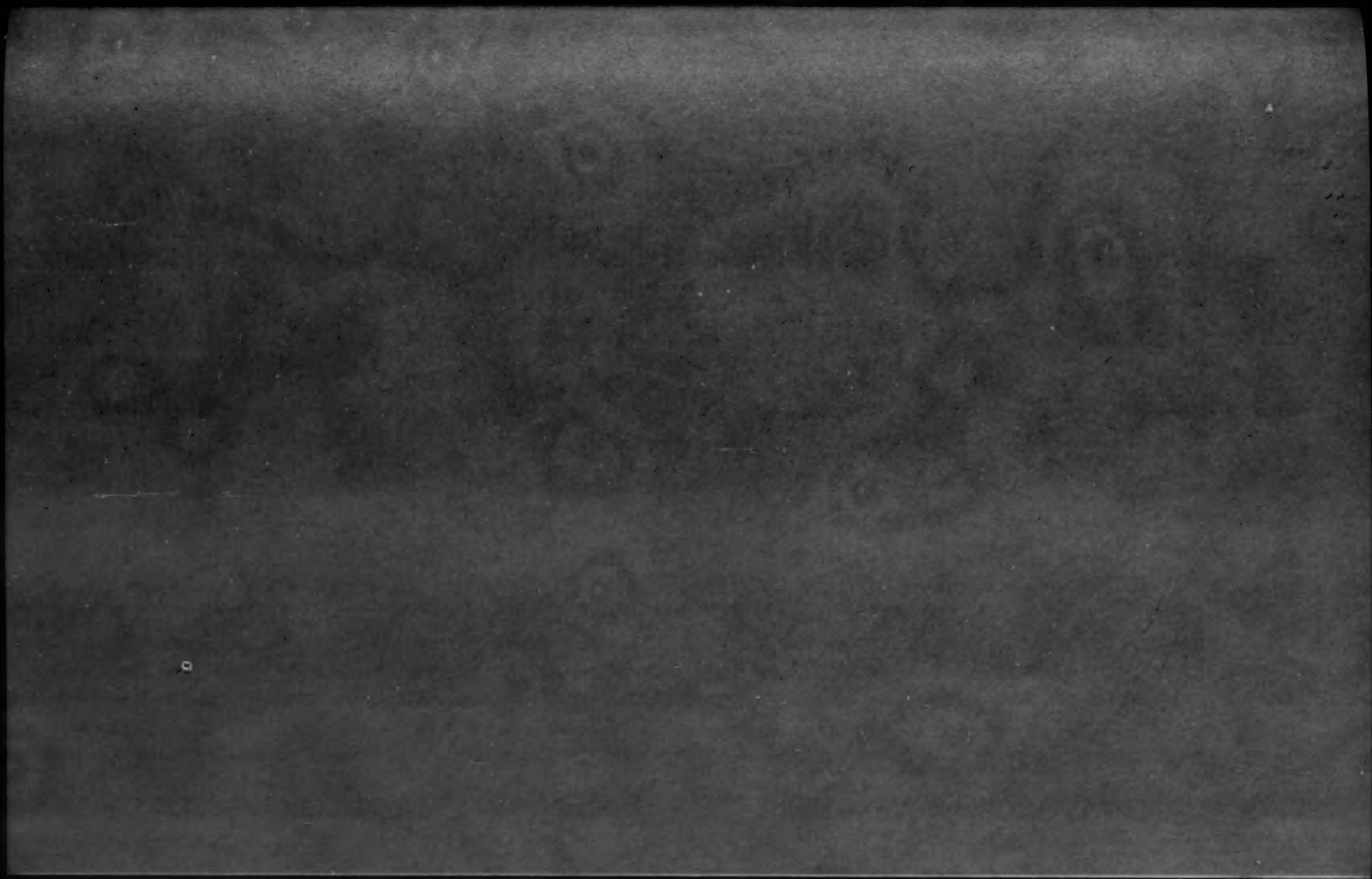

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

APRIL 1941

VIRUS INFECTIONS*

THOMAS M. RIVERS

Director, Hospital of The Rockefeller Institute for Medical Research

At the present time when one speaks of an infectious disease one usually thinks, because of habit, that such a disease is caused by a microörganism. As a rule, one does not stop to analyze just what one considers a microorganism to be, nor does one usually pause very long for thought about whether an infectious disease might be caused by an agent not classified as a microörganism.

For many centuries contagious diseases have been recognized, and infection was long an obvious fact before the cause of contagion or infection was known or understood. Then came the discovery of bacteria and protozoa; still considerable work had to be done over a period of many years with these tiny animals and plants before it was realized that they had anything to do with contagion and infection. The flowering of such an idea ushered in the microbiological era in infectious disease when it was firmly established that these maladies are caused by bacteria, fungi, spirochetes and protozoa. Indeed, it became so firmly established that these microörganisms produce infectious diseases that it was a heresy to consider them possible of causation in any other manner.

* Given October 23, 1940 in the Graduate Fortnight of The New York Academy of Medicine.

Long before the microbiological era in infectious diseases, a method of preventing one infectious malady had been devised and its usefulness thoroughly established. I am speaking of vaccination against smallpox. When it was shown that microörganisms cause disease, investigators attempted to find a bacterium or a protozoan parasite responsible for smallpox. In fact, many different kinds of microörganisms were described as the etiological agent of this malady, but no agreement was reached regarding any of them. In 1898, the filterable virus era was vigorously initiated by the discovery that tobacco mosaic is produced by an agent capable of passing through earthenware filters, impervious to ordinary bacteria. Shortly following this, numerous agents, including those of smallpox and vaccinia, were shown to pass such filters and to be so small that it was impossible to see them by means of ordinary microscopes.

Thus, there came into existence, in addition to bacteria, protozoa, fungi and spirochetes, a group of agents now known and spoken of as viruses. As soon as this group was recognized, there immediately arose lengthy discussions regarding the nature of its members and the character of diseases produced by them. These discussions are still in progress, but fortunately much of the mystery and misunderstanding about viruses is gradually being dissipated. Perhaps some of the mystery is due to the fact that the agents producing virus diseases are not visible. For unknown reasons, it seems difficult for certain students of infectious diseases to accept the idea that some of the most powerful agents in nature do not possess a size compatible with visibility, and they still believe that the cause of an infectious disease must remain unknown, unidentifiable and mysterious as long as it is invisible. Until such an attitude has been relinquished, it will be difficult for anyone to clear away the mystery surrounding viruses and virus diseases.

There is no mystery regarding the importance of virus maladies, because they have always been, and still are, very potent factors in the economy and physical well-being of all forms of life. Indeed, from the highest form of life, man, to one of the lowest, bacteria, each stratum is involved. For instance, millions of dollars are lost each year because of virus diseases of plants and lower animals. Virus diseases of tobacco, potatoes, corn, tomatoes, beets, lettuce and sugarcane make great inroads upon our sources of income. Foot-and-mouth disease of cattle, hog cholera, swine influenza, cattle plague, fowl pox, equine encephalomye-

litis, swine pox, infectious tracheitis of chickens and avian encephalitis are also costly maladies. Man is subject to smallpox, yellow fever, measles, chickenpox, poliomyelitis and several kinds of encephalitis. Even the lowly bacterium, without which life of all forms on this world would quickly become extinct and our planet would be within a short time as barren as the moon, is subject to its own virus disease, bacteriophagy. Even a casual survey of the diseases just mentioned is sufficient to impress upon anyone the reality of their importance and remove the notion that when an investigator talks about virus diseases he is dealing with something intangible and very mysterious.

The fact that there are infectious agents smaller than ordinary bacteria was discovered more or less accidentally through the use of filters specially designed to hold back bacteria while permitting the passage of their metabolic products, *e.g.*, toxins. The fact that these agents pass such filters led to their designation as filterable viruses. Filters can be made of all grades of porosity; in other words, there are filters with pores that permit the passage of bacteria, while others possess pores so small that ordinary proteins, as well as the viruses, are retained. It just happened that filters had been made to retain ordinary bacteria in order to separate their toxins from them. When such filters were used in certain kinds of investigative work, it was found that some infectious agents, capable of multiplication and for that reason not toxins, would pass through them. If other kinds of filters, that is very tight ones or ones with very small pores, had been used, the discovery of filterable viruses would have been delayed. Thus, the term *filterable virus* is somewhat misleading, because some viruses are difficult to filter, while a few very small bacteria are capable of penetrating certain of the more porous candles used in bacteriological work. At present most workers speak of viruses instead of filterable viruses, because of confusion caused by the word *filterable*.

The fact that most viruses go through filters which retain ordinary bacteria is evidence that they are smaller than such bacteria. How much smaller was not known for a long time. However, very soon it was realized that all viruses are not of the same order of magnitude, because certain of them pass filters that hold back others. Now we know the approximate size of a large number of viruses, and the diameters of these virus particles range from 250 mμ to 8 mμ. Some viruses, for instance, those of psittacosis and vaccinia, are on the border of visibility by means

of ordinary microscopes, while others, namely, those of poliomyelitis and foot-and-mouth disease, because of their small size, will never be resolved by means of ordinary light. The fact that viruses pass filters impervious to ordinary bacteria and are invisible by means of ordinary light in the unstained state, should not immediately lead one to believe that all viruses are alike in nature or that all of them are necessarily quite different from minute bacteria. Indeed, certain very minute bacteria, which are capable of cultivation on ordinary lifeless laboratory media, pass filters as readily as do the viruses of vaccinia and psittacosis. Insofar as size is concerned, there is no reason to believe that these bacteria are much more complex than are the viruses mentioned. On the other hand, when one considers the viruses of poliomyelitis and foot-and-mouth disease, it is very difficult to imagine that they are as complex as bacteria, because they possess diameters of approximately 8μ which are only slightly greater than those of certain protein molecules.

Until proper means of concentration and purification of viruses were devised, one was left with conjectures regarding the complexity of their components. Within the last ten years great strides have been made, and during that time a number of plant viruses and a few of the animal viruses have been concentrated and purified to such an extent that one is warranted in drawing certain conclusions from their chemical analyses. In addition, some of the plant viruses have been crystallized and have been shown to be large molecules of nucleoprotein containing yeast nucleic acid. When this discovery was made in 1935 by Stanley, many investigators immediately concluded that all viruses probably would finally be shown to be molecular entities, either small or large, somewhat similar to plant viruses. However, workers who have been studying the nature of vaccine virus, the infective unit of which is spoken of as an elementary body, have come to the conclusion that this particular virus is much more complex than that of tobacco mosaic, inasmuch as it is composed of several different kinds of protein, including a nucleoprotein with thymonucleic acid, neutral fats, phospholipids, and other substances as yet unidentified. In other words, some investigators are inclined to look upon the elementary bodies of vaccinia as structures possessing qualities unlike those associated with ordinary molecules.

The complexity of vaccine virus is discernible not only by chemical examination but also through immunological studies. In fact, it is at times easier to differentiate between two proteins by means of immu-

nological techniques than it is by those of chemistry. From the investigations of a number of workers, it has been definitely shown that there are several antigens associated with vaccinal infections and that they in all probability derive from the virus. Thus, it appears that there are at least two soluble antigens, one heat-stable, the other heat-labile, which occur separately or as a complex. In addition to these, there are at least two others which are intimately associated with the elementary bodies or virus, e.g., an agglutinogen and a substance that gives rise to neutralizing antibodies following an infection with the virus. A similar antigenic complexity has also been found in the viruses of infectious myxomatosis and psittacosis. In the case of these two diseases, however, antigens associated with the etiological agents have not been so thoroughly investigated as they have in vaccinia. The findings mentioned are quite different from those resulting from immunological investigations of simple viruses, e.g., that of tobacco mosaic which, so far as can be ascertained, is constituted of a single antigenic substance.

Most protozoa are easily visible and some of them are cultivable on artificial media containing no living cells. This is also true of the spirochetes. Fungi and bacteria are visible, and most of them have been cultivated on lifeless media. On the other hand, viruses, in addition to being invisible, are also uncultivable on lifeless artificial media; and, for that reason, many investigators concluded that there must be something mysterious about them and that of necessity they had to be different from ordinary microörganisms. Such a conclusion does not naturally follow, because there are bacteria which have not as yet been cultivated or induced to multiply outside of a susceptible host. The bacillus which causes leprosy is an excellent example.

It is true that no virus has as yet been induced to multiply in the absence of living host cells; but such a fact should not cast a veil of mystery over the virus group, because obligate parasitism is not an unknown phenomenon even among visible infectious agents, e.g., malarial organisms which multiply in a living host and not on lifeless artificial media. If some large infectious agents are obligate parasites, there is all the more reason for minute ones to require the assistance of host cells in carrying on the functions of life and multiplication. Indeed, beyond a certain point the smaller and less complex an infectious agent, the more likely it is to be an obligate parasite; because of minute size it would not be capable of possessing all the necessary con-

stituents for autonomous existence. This matter has been discussed at length by Green who believes that all viruses are obligate parasites, even those of molecular dimensions. Obligate parasitism implies life, and Green believes that the nucleoprotein molecules of tobacco mosaic virus are living. According to him, multiplication is the only activity of which such a molecule is capable; the remaining activities necessary for such a living entity are carried out by host cells.

I admit that Green's ideas are plausible, but whether his scheme accounts for everything in the virus field is still a problem. At least there are other workers who think that some viruses, if not all, are manufactured by their host cells. According to them, there are substances in host cells which are precursors of viruses and which are converted into the virus agents through the action of proper stimuli; at the moment the only effective stimulus that is definitely recognized is some of the virus which is to be fabricated. There are excellent examples in the enzyme field to warrant such ideas; for instance, trypsinogen *in vitro* is converted into trypsin by the presence of a small amount of trypsin. At the present time Krueger and Northrop are carrying on extensive investigations with bacteriophage in attempts to show that this agent has precursors which are transformed into the virus under certain conditions. Unfortunately, as yet the results of their work are inconclusive.

From what has been said it appears that viruses are smaller than ordinary bacteria, some being much smaller, even approximating protein molecules in size, and that they do not multiply outside of a susceptible host. Furthermore, the indications are that the multiplication occurs within the involved or affected cell regardless of whether it takes place in a manner compatible with ideas regarding obligate parasitism or by fabrication through the activities of the host, aided by the processes of autocatalysis. This means that there is a very close relationship between viruses and their host cells. This close relationship between the infectious agent and the host cell undoubtedly accounts for many of the characteristic features of virus diseases. However, one must not forget that, inasmuch as there are intracellular parasites other than viruses, such features are not necessarily limited to virus diseases. On the other hand, no group of infectious agents as a whole exerts all of its forces through intracellular activity, and in that respect the virus group is unique.

As a result of the close relationship between viruses and their host cells, one of three things or a combination of these three things may occur. Rapid growth of a virus may cause immediate death of infected cells, or multiplication of the virus may first stimulate the cells and then destroy them, or, finally, the virus may act in such a manner that only stimulation of cells takes place. As one examines pathological tissues from virus diseases one sees that the things just mentioned have happened. In yellow fever, Rift Valley fever and foot-and-mouth disease the rapid growth and explosive action of the viruses lead to a picture of necrosis. In smallpox, fowl pox, vaccinia, chickenpox, and certain other virus diseases one sees early in the development of lesions only stimulation of infected cells which accounts for the formation of papules; later the stimulated cells making up the papular eruptions undergo destruction producing pustules or vesicles. Finally, in such conditions as Rous' sarcoma of chickens, Shope's papilloma, and warts, stimulation of cells is a prominent, if not the only, feature of the pathological picture.

Inasmuch as mutiplication of viruses takes place within cells, it is not surprising that the phenomena just mentioned occur. In addition to this, in certain virus diseases inclusion bodies, which may or may not be made up of virus elements, are seen in the nucleus, in the cytoplasm, or in the nucleus and cytoplasm of infected cells. These inclusions are not necessarily pathognomonic of virus diseases, because some have been described in the absence of demonstrable viruses. Yet, as a rule, typical inclusions put the initiate on the lookout for a virus and at times may indicate the type of virus to be searched for; for that reason they are a great aid to virus workers.

Most physicians have been taught that inflammation is a prominent feature of infectious diseases. Inflammation occurs in virus diseases, but it is not a primary phenomenon; it is secondary to cell destruction. Many infectious diseases caused by agents other than viruses are characterized by an outpouring of polymorphonuclear leukocytes. In virus diseases, however, the inflammatory reaction is usually characterized by mononuclear cells. There are exceptions to the rule in both instances, and as yet one cannot account for the rule or the exceptions.

From what has been said about the close relationship between the host cell and virus agent, one might expect that viruses would exhibit selective localization; they do. Some viruses attack only certain hosts,

that is, they are quite host-specific. Not only are they host-specific, but frequently they attack only certain cells within these hosts. Indeed, a few investigators have attempted to classify viruses by the type of cell attacked, dividing them into epitheliotropic, neurotropic, endotheliotropic, mesotheliotropic, and pantropic agents. Such a classification, unless used very loosely, is not satisfactory, because, although there is a tendency for viruses to limit their activities to certain cells, only a few of them limit their attack to one kind of cell. Perhaps the best examples of the strict tropism of viruses are Shope's papilloma of rabbits which attacks only epidermal cells without involving the epithelial tissues of the buccal mucosa, and the wart virus of Kidd and Parsons which produces lesions in the epithelial cells of the buccal mucosa of a rabbit but not in those of the skin.

One must not entertain the idea that selective localization of infectious agents is limited to virus diseases, because a similar phenomenon is observed in other types of infection. It is well known that the meningococcus is likely to involve the coverings of the brain and cord, that the pneumococcus usually causes pneumonia, and that the typhoid bacillus generally produces an enteric infection. All the reasons for the selective localization of infectious agents, whatever their nature may be, are certainly far from being known.

Although viruses often attack more than one kind of cell, the clinical pictures produced by them for unknown reasons are usually consistent, thus enabling clinicians to make proper diagnoses with a fair amount of regularity. For instance, in spite of the fact that the viruses of measles, varicella and smallpox enter the susceptible hosts by way of the same portal and are distributed throughout the body by means of the blood, clinicians are usually able to distinguish between these three maladies. In view of the fact that viruses and other infectious agents exhibit selective localization and since some virus diseases can be diagnosed from clinical pictures alone, one must not immediately conclude that all virus diseases can be diagnosed without the aid of laboratory techniques. This is particularly true of infectious diseases of the central nervous system. In other words, one cannot forthwith differentiate between the pyogenic infections of the meninges without laboratory aid; nor can one on clinical and pathological grounds alone with any regularity correctly diagnose virus diseases of the central nervous system.

If it is difficult to differentiate one virus disease from another by

means of clinical observations alone, or if one encounters trouble distinguishing virus diseases from maladies caused by other kinds of infectious agents, how can these things be accomplished with precision? There is nothing mysterious about the matter; one goes about diagnosing virus diseases just as one proceeds in arriving at a proper diagnosis of other infectious maladies. The general principles are the same; the differences lie in the techniques used. In the first place, one attempts to isolate and identify the virus responsible for the trouble. Frequently this is possible, as in the case of psittacosis, yellow fever, rabies and influenza. At this point in the procedure the only difference between virus diseases and other infectious maladies is that one does not use ordinary lifeless media to cultivate and isolate a virus. Instead one employs living media, e.g., small laboratory animals, developing chick embryos, or modified tissue cultures.

Many of the viruses act in a characteristic way in the living media, and from this an experienced laboratory investigator obtains a clue as to the nature of the virus with which he is working. This is not unlike what the bacteriologist does when he makes cultures of microörganisms on agar plates or in broth; from the appearance of the colonies and by means of proper stains, etc., clues are gotten regarding what organism is being handled. From the appearance alone of a bacterium or from what a virus does in its living medium, one cannot be certain as to the identity of the infectious agent. In both instances it is necessary to proceed further through the use of different kinds of media, e.g., in the case of bacteria, media containing various sorts of sugar for fermentation tests, and in the case of viruses, different laboratory hosts for the establishment of the host range. Having done this, the worker has further information regarding the identity of the virus; still he may be unable definitely to classify the organism or the virus. At this point he turns for aid to classical immunological reactions. These are the same regardless of the type of infection being studied; agglutinations, precipitin reactions, complement-fixing reactions, and neutralization or protective tests are used.

Immunological principles are broad and are universally applicable provided one understands them and is ingenious enough to devise ways of applying them. Probably the first immunological phenomenon to be noted was in connection with virus diseases. Many centuries ago it was observed that individuals recovering from certain infectious mala-

dies, e.g., smallpox and measles, usually possessed a lifelong immunity. Such an enduring immunity is most striking in virus diseases, although it is known to occur in other infections. In the study of virus diseases use is made of this phenomenon in the identification of their etiological agents. Animals are infected with known viruses and after recovery they are inoculated with the unknown agent. If among the viruses used for the original inoculation there is an agent similar to the unknown, then the animal receiving that particular agent would be resistant to the unknown and in this way indicate the identity of the unknown. Such a procedure is not unique for virus studies, because it is used also for the identification of other kinds of infectious agents or their toxins.

During the last 100 years antibodies were recognized and came into use for the identification of infectious agents and for the diagnosis of infectious maladies. About forty years ago it was shown in regard to virus diseases, e.g., in the case of smallpox and vaccinia, that serum from a convalescent animal mixed with the virus responsible for the malady protects a susceptible or non-immune animal against the virus in the mixture. This procedure is known as the neutralization or protection test, and is used extensively in the identification of viruses and for the diagnosis of virus maladies. This test is not unique, because it is similar to those used for the identification of toxins, bacteria and the diseases caused by them.

The complement-fixation test was the next immunological reaction to be used in the study of viruses. Jobling, in 1906, showed that serum from an animal convalescent from a vaccinal infection upon being mixed with vaccine virus would specifically fix complement. In 1913, Paschen demonstrated that elementary bodies of vaccinia and smallpox were specifically agglutinated by serum from individuals convalescing from these infections. Then came the work of Craigie and others showing that in the case of certain virus diseases there are soluble antigens separable from the viruses themselves which precipitate in the presence of specific immune sera. These soluble antigens also fix complement under proper conditions. Thus, it is obvious that the immunological tests used in the study of virus diseases are in principle exactly like the ones employed in other infectious fields. All that is required is that one banish ideas of mystery and set oneself to the task of learning the details essential for success.

Now in regard to the treatment of virus diseases. Is there anything

peculiar about this aspect of the virus problem and is it different from those associated with other kinds of infectious diseases? With a few possible exceptions, one can immediately say, no. In spite of a few antibacterial sera and antitoxins, the treatment of bacterial infections until recently was largely expectant. Chemotherapy in the last few years has changed the whole picture. As yet, however, no great advance in this direction has been made in the virus field. It is true that certain reports have appeared stating that lymphogranuloma inguinale and trachoma are benefited by some of the sulfonamide compounds. Despite the meager results so far obtained, there is no reason to suppose that great advances in the treatment of virus diseases will not be made in the future by means of chemotherapy; indeed, this seems to be the most likely source of curative agents for this type of malady.

At the moment, the treatment of virus diseases in general is still expectant. One might inquire why serotherapy has not been successful in virus maladies. It certainly is not for the lack of intensive effort. Most of the virus diseases have been treated by immune sera, but unfortunately the results have not been encouraging. As one considers the problem in the light of what is known about viruses, one is forced to the conclusion that serotherapy of the diseases caused by these agents is not likely to yield desired results. A reason for this is found in the fact that viruses are intracellularly situated. Since antibodies do not enter cells, such a situation makes it impossible for the antibodies in therapeutic sera to reach the infectious agents. Still, one might well ask why antibodies therapeutically administered do not attack viruses as they leave infected cells on their way to attack normal cells not already involved. They do, because viruses in an extracellular location are susceptible to the action of immune sera. Then, why is it that immune sera are not efficacious in the treatment of virus diseases? A good deal of experimental evidence exists which indicates that in most virus diseases, by the time signs and symptoms of infection are manifest, all of the cells that are going to be infected in that particular host have already been entered. In view of such evidence, one would not expect serotherapy to be of great value in the handling of these maladies. Undoubtedly there may be exceptions to the statement just made, but one should demand adequate proof of the therapeutic efficacy of all antiviral sera.

In the prevention of virus diseases there is at the present time little

to offer except quarantine measures, and several convalescent sera. Indeed, most of the quarantine measures seem fairly useless. I doubt very seriously whether measles, chickenpox, poliomyelitis, influenza and smallpox are influenced in the least by the quarantine measures now employed. Furthermore, I do not know of any that would be of use under our present social conditions. Except for making people believe that public health officials are doing something, it would seem to me that money spent on many quarantine measures might be used better in other ways. I trust there comes a time when lay people will be sufficiently informed and possessed of sufficient stamina to demand of public officials that expensive and unessential things which interfere with business and social activities be not done.

Vaccines originated in the virus field. The first successful vaccination was carried out by Jenner when he prevented smallpox by the inoculation of human beings with vaccine virus. This was accomplished on an empirical basis long before bacteria or similar agents were known to be associated with infectious diseases. Vaccination against smallpox is still the outstanding method of preventing a severe infectious malady. In spite of that, perhaps 40 per cent of the people in the United States are at this moment susceptible to smallpox. Vaccination against yellow fever has been perfected within recent years and bids fair to control outbreaks of this malady, provided public officials and the lay people are willing to see it properly used. A vaccine for equine encephalomyelitis has been developed; and perhaps in Horsfall's recent work with influenza and distemper there lies a method of preventing influenza. Tests of this influenzal vaccine are now under way, but it will be sometime yet before an answer will have been obtained. There is every reason to suppose that eventually many more virus diseases will come under control through the use of properly prepared vaccines; and it is for this reason that investigators are willing to spend many tedious hours in carrying on work that frequently yields disappointing results.

How do viruses spread in nature? There is nothing peculiar or characteristic about the spread of viruses. Most plant viruses are spread by insect vectors. A few virus diseases of man are spread in this manner, e.g., yellow fever by the mosquito. Spread of the majority of virus diseases of man that we know about at the present time, however, seems to be accomplished through contact or by means of droplet infection. Of course this means that, unless one can sterilize and keep sterile the

air which one breathes daily, it will always be difficult to control virus maladies through sanitary measures alone.

Undoubtedly some will ask why is there nothing peculiar about the epidemiology or spread of virus diseases in a population, since some of the agents causing these maladies may be fabrications of their host cells. Regardless of whether viruses are minute obligate parasites or whether they are inanimate fabrications of host cells, no virus disease has as yet been shown to arise *de novo*. Every case of a virus disease results from the entry of the virus into a host from another host. Thus, the spread of virus diseases, as is the case with other types of infectious disease, is wholly dependent upon transmission of the inciting agent from one host to another. Epidemics of virus diseases do not arise as a result of multitudinous, simultaneous foci of *de novo* fabrication of their etiological agents. A statement of this kind does not imply that new infectious agents have not come into existence during the past or that no new ones will develop in the future. Yet, so far as I know, there is no evidence to show that a single absolutely new infectious agent has come into existence during the time covered by the recorded history of man.

Upon viewing the matter dispassionately one finds that in many respects virus diseases resemble other infectious maladies. Furthermore, it is obvious that such diseases, including those displaying neoplastic phenomena, truly belong in the large category of infections. That they should be looked upon as something strikingly peculiar or even mysterious is due to a state of mind instead of factual evidence. Perhaps such a mental attitude can be accounted for to some extent by unfamiliarity with the subject.

It is true that viruses differ from other types of infectious agents; but that can be said of each of the other types. In spite of the facts that viruses are invisible, that they multiply only in living susceptible host cells, that all of them may not be alike in nature, and that some are crystalline proteins, the problems resulting from the invasion of a single host by a virus or from epidemics of virus diseases, and the general principles underlying methods of solving these problems are similar to those encountered in other infectious fields. From a practical standpoint it makes little difference at the present time whether a virus is an inanimate crystalline protein or a minute obligate parasite. In fact, the actions of bacteriologists, epidemiologists, immunologists, physicians and public health officers would not be affected immediately by final deci-

sions regarding the nature of all agents now classified as viruses. On the other hand, knowledge obtained in arriving at such decisions would be of inestimable value at some future time not only in regard to a better handling of virus diseases but also in regard to a better understanding of general biological phenomena. For that reason many virus investigators are willing to toil without thought of immediate reward in the hope of eventually making a worthwhile discovery.

POLIOMYELITIS*

JOHN R. PAUL

Professor of Preventive Medicine, Yale University School of Medicine

SEVERAL different aspects of the poliomyelitis problem will be considered in this paper: first, the environment in which epidemic poliomyelitis seems to thrive; second, some clinical aspects of the disease; and third, theories which concern its mode of spread.

ENVIRONMENT

The picture in Figure 1 is a reminder that poliomyelitis is a summer disease, which flourishes in a rural setting. Actually the scene illustrates the site of the first reported case in a recent Connecticut epidemic,[1] but the general setting may be familiar to anyone who has had occasion to see many cases of poliomyelitis. It might be reduplicated over and over again during poliomyelitis epidemics in many States of the Union. There is, of course, no doubt that poliomyelitis epidemics are common enough in cities, but it is the frequent severity of the epidemics in the country that concerns us. Something important causes this disease to flourish in the country during the summer. This may be entirely due to an increased susceptibility among rural children, but in recent epidemics the age distribution of both rural and urban cases has been such as to render this explanation unlikely. Whatever the rural factor or factors may be, they have not received as much emphasis in this country as we believe they deserve, for they must be almost as fundamental, from the standpoint of etiology, as is the virus itself. In any event the recognition of the existence of these factors has led us to regard a local epidemic of poliomyelitis as an indication that the "place is infected," as well as some of the people in it. In other words we do not believe that poliomyelitis is a contact disease per se, but that the proper environmental setting is more important for the spread of the disease than is the mere presence of the virus among a group of susceptible children.

* Delivered October 23, 1940, in the Graduate Fortnight of The New York Academy of Medicine. From the Section of Preventive Medicine, Yale University School of Medicine.

Fig. 1—A picture of the rural surroundings in which epidemic poliomyelitis flourishes. The scene is taken from an actual epidemic. Some of the children shown here are convalescent from abortive attacks and are intestinal carriers of the virus. Note the open sewer emptying into the brook. Insert: outline map of the State of Connecticut.

Clinical Considerations

Clinical poliomyelitis may assume several forms but by far the commonest, is abortive poliomyelitis. It is also the most difficult to diagnose. There are no inexpensive diagnostic tests and no distinctive clinical features whereby abortive, or suspected abortive cases of poliomyelitis may be recognized; and so the clinician must fall back on his clinical judgment, which must be brought to bear not only on the patient but also on the circumstances under which these illnesses appear. For instance, when two children in the same family fall ill during a poliomyelitis epidemic with about the same symptoms, and after a day or two one child emerges from the illness with a paralyzed limb, whereas the other does not, it is fair to suspect that the milder illness of the two also may have been poliomyelitis (Fig. 2). And, as a matter of fact, it is occasionally possible to substantiate the diagnosis of abortive poliomyelitis by laboratory determinations, if one is fortunate enough to be in touch with a laboratory that can perform these time-consuming, difficult, and expensive tests. Perhaps it may seem like a waste of time to be placing emphasis on the mild form of the disease, but without an appreciation of the

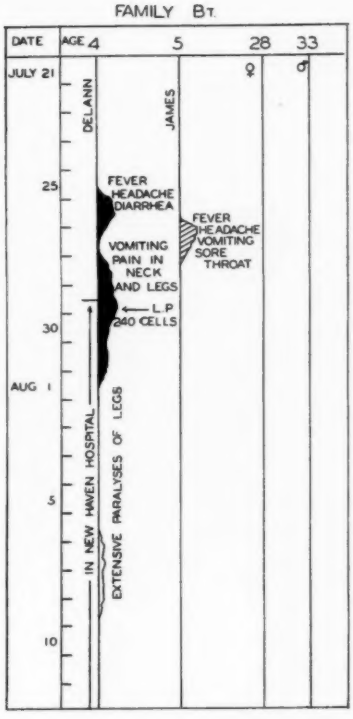

Fig. 2—Diagram of a fairly typical family with poliomyelitis. Vertical lines indicate the family members, their ages appear at the top. Both children became ill at about the same time; eventually one became paralyzed. The presence of paralysis aids in the clinical diagnosis but it does not aid in determining which of the two children will excrete the most virus in their stools.

concept of abortive poliomyelitis it is harder to grasp the real significance of this disease. The parents of a family of children can perhaps afford to be interested only in paralysis, but not so the physician. His best chance of discovering the true incidence of infection is to observe the abortive as well as the paralyzed cases. As abortive cases outnumber the paralyzed cases by 4 to 6 times in some epidemics,[2] they can also be a tremendous source of virus in the community. It may be recalled, for instance, that both types of poliomyelitis cases may harbor large amounts of virus in their stools, particularly during the first three weeks of convalescence. But the abortive cases may scatter the virus more widely, for unlike the paralyzed case which is confined to bed, either at home or in the hospital, during this period, they are allowed to roam about at will as soon as their brief period of fever is over (Fig. 3).

Symptomatically the mild abortive case is characterized as a brief illness, usually with fever lasting from a few hours to a few days, which

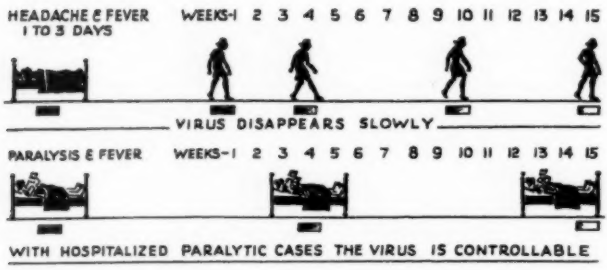
ABORTIVE CASES OF POLIOMYELITIS
ARE MILD AND ACT AS HEALTHY CARRIERS
HEADACHE & FEVER
1 TO 3 DAYS
WEEKS-1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
VIRUS DISAPPEARS SLOWLY
PARALYSIS & FEVER
WEEKS-1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
WITH HOSPITALIZED PARALYTIC CASES THE VIRUS IS CONTROLLABLE

Fig. 3—The ambulatory patient convalescent from an abortive attack can act as a widespread source of virus in the community.

is accompanied by one or more of the following symptoms: fever, headache, vomiting, lassitude, occasionally sore throat, and occasionally diarrhea, often a little pain in the back and occasionally a stiff neck. When I speak of fever I mean a temperature of 101° or more, which is unexplained on any other basis; and when I refer to pain in the back, it is well to recall the spine sign as the most valuable method for its detection. The lumbar puncture nearly always yields negative results in these cases. These diagnostic aids sound vague, but in spite of the non-specific character of this illness the diagnosis of abortive poliomyelitis is made with more confidence and more often today than it was ten years ago. The practical lesson is that, during a poliomyelitis epidemic, all children who suffer from a nondescript febrile illness should be put to bed for a longer period of time than is done under other circumstances. This should be done cautiously, and with every effort to allay a hysterical response on the part of the parents of the patient, but actually such patients should be treated with almost the same solicitude as the paralyzed ones; for how can one tell when an abortive case is going to turn into a paralytic case. This brings us quickly to a consideration of the treatment of choice during the so-called preparalytic phase.

I hesitate to recommend any definite therapeutic course but will merely describe what we do, at present, and why we do it. In principle we follow the same measures that are employed in the early stages

of any brief febrile infection, but in this disease we try to guard the patient carefully, and to protect him from all forms of *meddlesome therapy*. We are apt to prolong the period of bed rest beyond that which is ordinarily employed. [If the patient does develop paralysis, the physician's task, of course, is to assist in allaying irritability; to protect weak or paralyzed limbs; and to support any impaired functions of the body, such as difficulty in voiding, in swallowing, or in breathing. After the active stage of paralysis is over, the management of poliomyelitis patients becomes largely a problem in orthopedics.] But the reason we do so little in the early stage is to avoid the possibility of harmful procedures. Clinical judgment (and we have no statistics to prove this) indicates that trauma of almost any kind may often turn a case in the wrong direction. Among traumatic procedures, I would include: unnecessary vena punctures or lumbar punctures; the administration of strong purgatives; the injection of foreign protein; and (with reservation) even the injection of human serum. The point is, that when a child's fate is hanging in the balance as to whether the virus is going to damage the central nervous system severely or not, it seems better to do nothing, rather than to do something which may not only be of unproven value, but also may fall under the category of a traumatic procedure. In support of this thesis, the best series of cases on record, that is the series with the lowest mortality and the lowest incidence of paralysis, received nothing but bed rest.[3]

As for the question of serum therapy we could easily devote our full period of time to a discussion of the pros and cons of this subject but I will dispatch this difficult question with the brief statement that at the New Haven Hospital we do not use serum at present; I do not wish to imply that it should never be used.

So much for therapy; next, what are the physician's duties with regard to prophylaxis? This is a subject which most authors would like to avoid; in any event, it is well to appreciate that the procedures are certainly subject to change from year to year. We believe that when poliomyelitis appears in a community it is wise to seek the immediate advice of the local health officer so that a uniform plan may be adopted in which all local physicians may join. The usual questions to be decided are: What should the attitude be with regard to the abortive case? Should the stools of all patients be disinfected, as in typhoid fever? Should the schools be opened, or closed? Should one advise that all

drinking water be boiled? Should one advise people to leave town? Should one advise the use of "antiserum" as a prophylactic measure? The answers to these questions are difficult indeed and they depend on the local situation, but there are two recommendations perhaps which are not local. First, it seems reasonable to discourage swimming in epidemic areas where the water has a possibility of being contaminated with local sewage. In justification of this recommendation I may say that there is little or no proof that poliomyelitis has ever been actually contracted from swimming; but there is proof that during epidemics, virus has been detected in sewage.[1,4] The thought of allowing children to bathe in virus polluted waters is, at least, unpleasant. Second, a ban should be put on all tonsillectomy operations during the epidemic period —A tonsillectomized child may fall into the category of a "traumatized" child; evidence points to the fact that the disease is more severe in a child whose tonsils have been removed within a year than in control children.[5]

Modes of Spread

Next as to current theories about the portal of entry of poliomyelitis virus in man. This is a controversial question and the best that we can do is to mention a few of the theories. For at least 20 years the belief has been widely held in this country and elsewhere, that poliomyelitis was a contact disease, spread perhaps by droplet infection; that poliomyelitic virus penetrated the nasal mucosa and entered the human body through the olfactory bulbs. One may recall that this theory gained popularity because it had been found experimentally that poliomyelitis could be produced by instilling the virus into the nose of the monkey. However, years later it was discovered that this technique was effective in other diseases too. For instance, it is now recognized that mice can be infected by the nasal instillation of yellow fever virus and rabies virus. Yet neither of these experimental procedures with mice tells us about the manner in which man acquires yellow fever or rabies. And so the original interpretation of the nasal experiments with poliomyelitic virus in the monkey begins to lose some of its force. One cannot deny that the nasal theory is possible, but we recognize today that there may be a number of ways whereby the virus may enter the body and, of these, the nasal route seems to be the most unlikely in man. The main evidence on which this last statement is based comes from the work of Sabin and Olitsky,[6] and

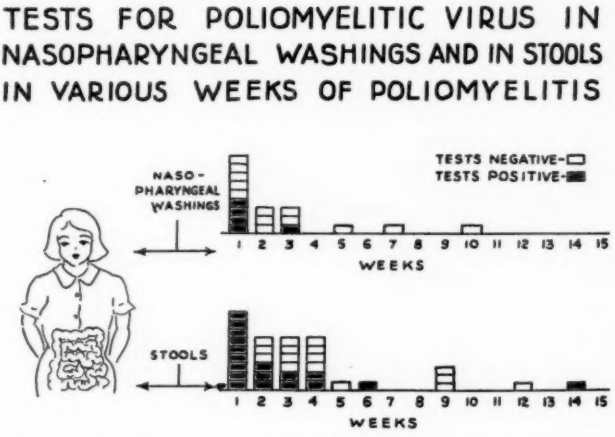
TESTS FOR POLIOMYELITIC VIRUS IN NASOPHARYNGEAL WASHINGS AND IN STOOLS IN VARIOUS WEEKS OF POLIOMYELITIS
TESTS NEGATIVE-
TESTS POSITIVE-
NASO-PHARYNGEAL WASHINGS
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
WEEKS
STOOLS
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
WEEKS

Fig. 4—The virus can be detected in the stool more readily than in the nasopharynx, and it persists for longer periods there.

others who report that human autopsies have so far failed, almost universally, to reveal those lesions in the olfactory bulbs which occur with such regularity when the disease is produced experimentally in the monkey by instilling the virus into the nose. The increasing number of negative olfactory bulb findings in human autopsies therefore indicates that portals of entry other than the nasopharynx exist in the human disease, although the nasopharynx has not been eliminated. As a matter of fact, poliomyelitis actually can be produced in man (as in the monkey) by an "extranasal" route, namely, by injecting virus under the skin. This was done accidentally, of course, when vaccines were being tried as a prophylactic measure in this disease some years ago.[7]

The next question which naturally follows a discussion of the portal of entry concerns the portal of exit of the virus. As you know poliomyelitis virus has been recovered from both the nasopharynx and the intestinal tract during acute and convalescent stages of the clinical disease. It is easier to recover virus from the intestinal tract than from the nasopharynx, and in both paralytic and abortive cases it persists there for longer periods of time, [8,9] (Fig. 4) and, thanks to a new and simplified technique of Howe and Bodian,[10] the stool is now becoming a diagnostic measure in this disease.* Regardless, then, as to where the portal of

* Howe and Bodian found that the instillation of small quantities of stool suspension into the nose of monkeys, could induce experimental poliomyelitis in 10 out of 14 cases.

entry of the virus is, an important portal of exit is the anus. Furthermore, as poliomyelitis virus is also very resistant (for one may recall that it withstands 1 per cent phenol, or 15 per cent ether), it is not remarkable that under certain circumstances this virus should appear in sewage. Other pathogenic agents may also be found in sewage, notably tubercle bacilli, and so the mere presence of poliomyelitic virus in this medium tells us nothing about the way this disease is spread; but it is interesting to know that it is there, and that it may be there in such large amounts, for one determination made during the 1939 epidemic in Charleston, South Carolina indicated that more than 18,000 doses infective for the monkey, were passing through one particular sewer each minute of the hour on which the test specimen was taken.

To summarize our views on the unsettled question of the modes of spread we believe then, that the nasopharyngeal portal of entry in the human disease is unusual; and we believe, as do others, that poliomyelitis is probably transmitted from one person to another through a number of different channels. Among these, may be that of close and intimate contact, but the situation is certainly not so simple as to be explainable on the basis of direct contact alone. Furthermore, it would seem unlikely that poliomyelitis is a true water-borne disease, for again the situation is not so simple. Whatever the real epidemiological situation may be, it is likely to be a complex conditioned largely by summer weather and aided by rural environment. One may recall in this connection that the presence of virus in sewage or water allows it to come in contact, particularly during the summer, with an immense number of living things. It again raises the question as to whether there may not be an extra-human host or hosts in this disease, in which insects, mammals or birds may play a part. As yet there is no real evidence for this, but the circumstantial evidence for an extra-human reservoir of virus in this disease is at least good.

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EPIDEMIC INFLUENZA*

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IN 1933, Smith, Andrewes and Laidlaw[1] announced that they had isolated from the nasal washings of influenza patients a virus which was pathogenic for ferrets by the intranasal route. The following year this observation was confirmed in our laboratory where strains of the same virus were recovered from epidemics in Puerto Rico,[2] the United States[3] and Alaska.[4] At the same time it was found that mice were also susceptible to the virus infection when anesthetized and inoculated intranasally.[2,5] Since then, the virus has been clearly established as the causative agent of epidemic influenza by the application of experimental methods to the study of individual cases in different epidemics.

THE DIAGNOSIS OF EPIDEMIC INFLUENZA

The laboratory diagnosis of epidemic influenza has employed essentially two approaches. The first, consisting of the isolation and identification of virus from the patient, is perhaps the most conclusive but also the most tedious and expensive. Commonly, the nasal washings of the patient are passed to ferrets and subsequent transfer of the virus is made to mice, where it can be satisfactorily identified by serological means. One can, however, allow the inoculated ferret to recover. In this case the presence of virus in throat washings is demonstrated by the appearance of antibodies to the virus in the animal's serum or in its capacity subsequently to resist active infection with known virus. Either method yields valid evidence of the presence of virus when positive; negative results are somewhat less significant.

The second approach makes use of the fact first demonstrated by Francis and Magill[3] that infection of human individuals by the virus of epidemic influenza calls forth a sharp rise of antibodies in the convalescent serum. While it is known that antibodies are detectable in a large proportion of normal sera, by comparing serum taken from the patient

* Delivered October 17, 1940, in the Graduate Fortnight of The New York Academy of Medicine.

during the acute phase of illness with that taken after recovery, the increase in titer can be measured. Two techniques are available: (1) the determination of the smallest amount of serum capable of protecting mice against fatal infection with a constant amount of virus, thus measuring the titer of neutralizing antibodies; (2) the determination of the smallest amount of serum which fixes complement in the presence of a constant amount of virus antigen prepared from infected mouse lungs or tissue culture medium.

Efforts have been made to gain knowledge not only concerning the frequency of virus infection in typical cases but to study the marginal cases as well, hoping in this manner to map the boundaries of the clinical picture. These observations have also served, reciprocally, to establish the value of the laboratory procedures for practical clinical purposes.

In order to demonstrate the frequency with which influenza virus can be identified in epidemic influenza patients, it will be well to summarize the experiences of various investigators in the winters of 1936-37 and 1938-39. Together with Magill, Rickard and Beck,[6] at the laboratories of the International Health Division, during the epidemic period from December 1936 to March 1937, material for study was obtained from 100 patients in whom a final diagnosis of epidemic influenza was made. Throat washings from 64 of them were tested by ferret inoculation and in 52, or 81 per cent, the presence of virus was demonstrated. From 23 of the washings, strains of virus were actually established in mice. In England, Stuart-Harris, Andrewes and Smith[7] similarly reported 75 per cent successful tests for virus from 40 typical cases although the number of strains transferred to mice was low. Moreover, in numerous other laboratories throughout the United States, Europe and the Far East, additional strains of the virus were recovered. Thus, from an epidemic of moderately severe influenza, pandemic in its distribution, the presence of the virus was demonstrable with relative ease in a high proportion of the patients attacked.

The results of 1938-39 offer an interesting contrast. The disease was not prominent in the general population but appeared more in the form of institutional outbreaks. Moreover, the clinical attacks were quite mild. Stuart-Harris, Smith and Andrewes[8] reported the recognition of influenza virus in only 7 of 59 throat washings obtained in 12 institutions. All of the positive results were had in late February or March. The strains of virus were of low pathogenicity for ferrets and were

adapted to mice with difficulty. Horsfall, Hahn and Rickard[9] studied 4 localized epidemics in January to March 1939. Throat washings from 65 cases were subjected to repeated ferret passage. Of these, 14 gave rise to antibodies in the ferret and 9 strains were adapted to mice. Our investigations in the same period apply more to the general population. No epidemic was recognizable. Throat washings were obtained from 28 selected patients among the nursing staff and patients on the wards of the Third Medical Division of Bellevue Hospital. In 3 instances the presence of influenza virus was shown by the development of antibodies in the inoculated ferret.[10] No strains were established in mice. In Australia, Burnet and Lush[11] reported the isolation of mild strains of virus in July 1939.

Hence, in the early months of 1939 when mild isolated outbreaks were observed in different parts of the world the virus was less readily isolated and the incidence of detection was approximately one-third that noted in the more severe outbreak of 1936-37. The uniformity with which virus can be recovered appears, therefore, to be related to the pathogenicity of the prevalent strains of virus and it becomes obvious that this procedure is unsuited to the diagnosis of a large number of individual cases.

Serological studies were also carried out in relatively large numbers of patients. Their value was established by a consideration of the results of the neutralization or complement fixation tests in relation to virus identification. Thus, in 1937 titrations of neutralizing antibody were made with acute and convalescent sera of 41 patients from whose throats virus had been recovered.[6] In each instance a sharp rise in the titer of the convalescent serum was observed. The average titer in the early days of illness was 22 while in convalescence it reached the high level of 235. The uniformity of response indicated that the virus infection and the increase in titer were associated phenomena. When comparable antibody responses were observed in the sera of patients from whom either virus was not recovered or throat washings were not collected, it was reasonable to conclude that the rise of antibodies was due, nevertheless, to infection by the same virus. Conversely, those cases of various clinical types, from whom virus could not be recovered and whose convalescent titer was essentially unchanged from the normal level were considered to have suffered from infections of different etiology. The results of the neutralization tests were verified by Stuart-Harris, An-

drewes and Smith[7] in a study of sera from 23 patients in the English epidemic of that year.

Following a procedure similar to that described by Fairbrother and Hoyle[12] the same sera were then tested in the complement fixation reaction.[6] Results, strikingly comparable with those of the neutralization tests, were obtained. An average rise in titer of tenfold to twentyfold was recorded in sera from the groups of patients which had yielded the positive neutralization tests. The groups of sera which yielded negative results by the neutralization test revealed no significant change in the complement fixation titers.

Hoyle and Fairbrother[13] had also noted the rise in complement-fixing antibodies during convalescence in 8 patients and observed further that the titers of convalescent patients were, in general, considerably higher than those of the general population tested immediately prior to the epidemic.

In the mild epidemic of 1938-39, when the incidence of virus detection was low, the serological tests maintained their efficiency in identifying cases of the disease. Stuart-Harris, Smith and Andrewes[8] were, by the neutralization test, able to demonstrate the occurrence of epidemic influenza in 4 institutions when virus was not isolated. At New York University virus[10] was demonstrated in only 3 of 28 patients. Acute and convalescent sera were obtained from 14 of the patients, however, and half of them showed the characteristic rise in neutralizing antibodies. The extensive studies of Horsfall, Hahn and Rickard[9] during the same period are extremely noteworthy. While in only 21 per cent of throat washings tested was the presence of virus proven, neutralization tests with the sera of these patients revealed a diagnostic increase of antibodies in 93 per cent. But, strikingly, in only one of 83 patients with non-influenzal respiratory infections was a comparable mounting of the titer observed. This shows clearly the significance of the test in establishing the etiology of the disease in a large group of patients which otherwise would not have been identified. The value of the serological reactions has thus been tested in two epidemics of greatly different severity and extent. One, with a high incidence of infection in the general population, pandemic in distribution, demonstrated the causal relationship of virus infection and positive serological tests; the other, recognized primarily in institutions in this country and abroad, was caused by virus which produced a mild illness, and was of low pathogenicity

for animals. In this outbreak the significance of the serological tests was enhanced, for, while virus was isolated from only a minority of cases, the circulating antibody titers identified the individual case just as accurately as in the preceding epidemic.

The investigations have confirmed the accepted theory that influenza is an epidemic disease in which a high proportion of cases presents a great uniformity of symptoms. It has been demonstrated, however, that distinct variations may occur. Thus, in 1936-37 in a group of contacts who exhibited no signs or symptoms of the disease, serological studies revealed that approximately 25 per cent had actually undergone virus infection. A similar incidence is recorded by Horsfall, Hahn and Rickard[9] in 1939. The importance of clinically undetected cases as agents of dissemination becomes apparent.

Certain information has been gained concerning the so-called relapses which some authors have considered a characteristic of epidemic influenza. There is ample evidence that serious pulmonary disease may follow what appears to be simple influenza. The most common is a mild bronchitis or bronchiolitis which develops slowly as the acute illness subsides. The usual story of the relapse is, however, that about the time of recovery the patient has a recurrence of fever and may then develop pulmonary disease. Numerous observers have considered such episodes to be secondary infections and the evidence of the virus studies clearly supports this conclusion. In 1936-37 we had the opportunity of studying material from 7 such patients.[6] They gave histories of moderate illness for 6 to 8 days and a sudden exacerbation of symptoms and fever prior to their admission to hospital. Bacteriological diagnoses of atypical pneumococcus pneumonia had been made in 2, acute pneumococcal bronchitis in 1, hemolytic streptococcal tracheitis in 1; 3 were simply called relapses of influenza. At the time they were first observed in the hospital, the serological tests revealed high antibody titers quite characteristic of the patient convalescent from virus infection. Virus was not detected in the 3 throat washings tested. It is evident, therefore, that the relapses were bacterial infections developing in convalescence from the virus disease. Stuart-Harris[7] has recorded relapses due to pulmonary disease in 3 patients and in 5 others due to acute hemolytic streptococcal tonsillitis. Cases of this general character illustrate clearly the lack of reason in considering the relapse a recrudescence of the primary virus infection. They are obviously caused by secondary bacterial invaders.

The same comment applies to the post-influenzal pneumonias occurring within a short interval after recovery. On the other hand, the British group[7] have reported the isolation of virus from 3 patients dying of pneumonia within 5 days of onset of influenza. In all of them cultures of the lungs revealed heavy growth of Staphylococcus aureus as well. We also[6] recovered virus on the second day of the disease from a patient with a simultaneous bacterial infection due to Pneumococcus Type III. This indicates that the possibility of severe respiratory disease beginning synchronously with the onset of the virus infection is an attribute of the bacterial agent. It is noteworthy that through the epidemics discussed, bacteriological studies have not disclosed a preponderance of a particular organism. In fact, the great majority of cultures have resembled the normal nasopharyngeal flora. It seems likely that the differences in mortality in different epidemics depend upon the nature of the bacteria prevalent at the time and that any of the common respiratory pathogens may be responsible for the serious complications.

Recognition of the average cases in the course of an epidemic is aided by their relative uniformity. A sudden onset is the rule, with fever and constitutional symptoms in the absence of prominent respiratory complaints such as the sore throat of tonsillitis or the nasal discharge of the common cold. The course is short and convalescence is relatively prompt except for residual fatigue. Either leukopenia or the absence of leukocytosis in the early days is a significant observation. Nevertheless, a diagnosis of epidemic influenza in the individual patient, considered out of relation to an epidemic, can not be made purely on the basis of clinical observation. In fact, the readiness with which a diagnosis of influenza is made under these conditions is inversely proportionate to the physician's diagnostic accuracy. Because of this, the early cases of an epidemic in a general population are usually recognized in retrospect. Moreover, epidemics and outbreaks of diseases as remote as yellow fever and lymphocytic choriomeningitis have been so diagnosed. These facts illustrate the relative non-specificity of the symptom complex.

Just as the confirmation of clinical diagnosis in so many illnesses depends upon the use of laboratory aids, so is it in epidemic influenza. Only with increasing efforts to establish the diagnosis etiologically will the clinical problem be solved. One can point out certain differentials which should be made and maintained. Epidemic influenza applies to

the disease in its abrupt epidemic form; there is no evidence to date that sporadic cases of the virus disease occur except in relation to an epidemic period. It is essentially a febrile, prostrating, brief disease; it is not the afebrile common cold with profuse discharge but with few constitutional symptoms; nor is it the purulent complication of the common cold. In acute pharyngitis, tonsillitis or sinusitis caused by the hemolytic streptococcus, pneumococcus, staphylococcus or Pfeiffer's bacillus the organisms can be identified, if the effort is made; these are not epidemic influenza. While a certain number of patients with epidemic influenza may have gastrointestinal disturbances, as is the case with numerous acute infections, there is little justification for the term, intestinal flu; etiological investigations have usually revealed food or water borne infection in outbreaks so designated.

There is in addition that group of irregularly distributed, low-grade respiratory infections of the winter season which the British writers have called febrile catarrh.[7] They bear little close resemblance to typical epidemic influenza but more probably represent bacterial infections of low pathogenicity and transmissibility. The use of the term, febrile catarrh, may well be a suitable one provided there is at the same time an admission that it is merely descriptive. No single etiology for these cases has been recognized.

Mention must also be made of certain epidemics bearing a close resemblance clinically and epidemiologically to those caused by the virus of epidemic influenza but in which all reported studies have failed to implicate that virus. One such epidemic was widespread throughout the entire United States early in 1936,[4] another this year. These outbreaks have recently been shown to be caused by a new type of virus[14] clearly different from that previously recognized. The entire field must, therefore, be reinvestigated in this light.

I have tried to show how the investigations to date have established the virus etiology of epidemic influenza and to summarize representative results from which that conclusion is drawn. Through the methods outlined a definitive picture of the disease and its variations is taking form. In this instance, as so often before, the establishment of diagnosis on the basis of etiology is serving to bring order in a field of infection which has been the source of marked clinical confusion.

To many minds the term, epidemic influenza, connotes only the devastating disease of the autumn of 1918. A survey of the history of

influenza reveals on the contrary that the world-wide scourge of 1918 looms from the pages of history as an episode without counterpart in the centuries through which physicians have recorded the characteristics of its not infrequent visitations. It was not unique in its spread throughout the world; it was not unique in the proportion of the population attacked or in the fact that it was looked upon as something entirely new to that generation of physicians. The rate of dissemination, the frequency of severe pneumonias which accompanied it and the mortality rate were, however, unprecedented.

It is well to recall that the autumnal outbreak of that year did not arrive unheralded. In the winter of 1915-16 an extensive epidemic took place. The influenza of the spring and summer of 1918 differed in no essential feature from that of recent years. Furthermore, practically all observers refer to the uncomplicated cases in the autumnal wave as 3-day fevers and it should be remembered that they constituted 80 to 90 per cent of the total in 1918. In other accepted pandemics the percentage of complications was extremely low, even though the incidence of disease was high. Thus, the term, pandemic, is not synonymous with high mortality.

It is my firm belief that the epidemics of varying extent which occur from year to year are the typical disease and that an episode such as that of the fall of 1918 represents a bizarre occurrence due probably to a simultaneous visitation of virulent influenza virus and a widespread dissemination of highly invasive bacteria of various species. Hence, the results of recent investigations, seeking insight into the accepted and debated opinions, appear applicable to the problem of influenza as a whole.

Measures Toward Prophylaxis or Therapy

Early in the course of virus studies attention was attracted by the fact that when large doses of active influenza virus were given to experimental animals by routes other than the intranasal, characteristic infection did not occur. Nevertheless, animals developed antibodies and became immune to virus given by the usual mode of inoculation. Furthermore, Shope[15] demonstrated with swine influenza virus that, in ferrets, subcutaneous vaccination elicited an excellent antibody response and that when such animals were subsequently infected intranasally, they were protected against pulmonary invasion even though a febrile

reaction and some nasal signs developed. These results have been amply confirmed with human strains. Furthermore, it has been practically impossible to recover virus from animals so treated, showing that vaccination increases the capacity to dispose of the infectious agent. These observations suggested that a similar series of events might be induced in man. In 1935 we conducted experiments to test this hypothesis.[16] It was found that the subcutaneous injection of relatively large amounts of active virus did not induce clinical infection in human subjects but that a sharp rise in circulating antibodies occurred. Since a rise in antibodies occurs as a result of infection and is associated with the immunity of convalescence, it seemed probable that the rise which followed vaccination also indicated the development of an increased resistance.

In this country an evaluation of subcutaneous vaccination of active virus as a measure protective against the natural disease in man has been attempted by Stokes and his associates[17, 18] and by Siegel and Muckenfuss.[19] The results have not justified a straightforward conclusion. In 1936 the figures obtained by Stokes and others, suggested a beneficial effect but subsequent studies have not been easily interpreted. Siegel and Muckenfuss in 1938-39 failed with the material they used to observe a satisfactory antibody response and, as would be expected, no statistically significant protection was noted. Thus, the procedure has not proven itself and the results so far have not been conclusive enough to permit any verdict. Under proper conditions, involving the use of a sufficiently good virus preparation to function as a proper antigen, and the coincidence of a well established outbreak of epidemic influenza in the test community, evidence will be gained, but not otherwise.

In England a vaccine of formolized inactive virus has been shown by Andrewes and Smith[20] to give rise to immunity in mice inoculated intraperitoneally and also to induce the formation of antibodies in human subjects. Nevertheless, the immunity has not been as firm as that produced by active virus. The results of its application to man have yielded no indication of protection against the natural disease.

More recently, Horsfall and Lennette[21] have reported the enhancement of immunity to influenza, in ferrets vaccinated with mixtures of inactivated influenza and canine distemper viruses. This interesting phenomenon is being intensively studied.

Despite the lack of information there has been a lurking suspicion that the subcutaneous injection of active virus would not be entirely

satisfactory under the most careful conditions. After all, it is clear that ferrets do not develop a complete immunity, and even in mice the resistance acquired as a result of subcutaneous vaccination is never as great as that which follows intraperitoneal immunization. Because of this we have been led to further consideration of the use of the nasal route for prophylactic procedures. The fact that subclinical infection in epidemic periods is common and the fact that the mere presence of antibodies is not synonymous with immunity have been well established. It seemed not unlikely that agents active in the nose might be important factors in determining clinical response since this is the primary point of attack of influenza virus. Together with Stuart-Harris[22] it was demonstrated that ferrets recovering from virus infection developed a new type of transitional-squamous epithelium which was resistant not only to virus but to severe physico-chemical injury with zinc sulphate ionization as well. Unfortunately, the change was not a permanent one but the respiratory mucous membrane was so conditioned that repair following reinfection was markedly accelerated. The possibility exists that changes of this sort bear some relation to the variations in resistance of different individuals and that these modifications could be influenced and maintained by nasal vaccination.

In addition, studies in our laboratory[23] and that of Burnet[24] have revealed that the nasal secretions of human subjects may contain a substance capable of inactivating relatively large amounts of the virus of epidemic influenza. A wide variation in the inactivating capacity is seen in the secretions at different ages or in different individuals of the same age. Since both the cellular factor and this serological factor are resident in the nose where the virus initiates infection, it may be that the local introduction of virus antigen by stimulating these mechanisms might produce more benefit than would accrue from simply increasing antibodies in the general circulation. Experiments to investigate these possibilities are being carried on at the present time. It has been found that as much as 10,000 mouse-lethal doses of virus cultivated in tissue culture medium can be given intranasally to human subjects without producing infection.[25] To what extent immunity develops has not yet been ascertained. It may be that only those whose nasal secretions are devoid of virus-inactivating substances need be subjected to immunizing procedures.

While it is apparent from this recital that prophylaxis against the

virus of epidemic influenza in man is in the experimental stage, the outlook on theoretical grounds appears quite promising. The procedures which are being carried out have a firm and clear-cut foundation in the results of animal experimentation. One difficulty which I do not propose to discuss at present is that strains of the virus may differ. If, however, an effective method of producing immunity against any one strain is established, the rest will follow. As previously stated, one of the chief obstacles to proper evaluation is the lack of coöperation on the part of the disease itself, in not presenting itself in the desired spot at the desired time.

Thus, while attempts to devise a satisfactory prophylactic procedure are being carried out, other efforts are also going on which may have a bearing on clinical therapy of epidemic influenza. It has been shown repeatedly that the injection of potent immune serum intraperitoneally into mice will give excellent passive immunity. More recently, Smorodintseff,[26] and Stokes, Henle and Shaw[27] have reported the fact that when the serum is given by the intranasal route even as late as 24 to 48 hours after infection of mice, fatal outcome may be prevented. These indications are suggestive. Certain clinical observations of 1918 also contain hints that convalescent serum may be of benefit.

On the other hand, chemotherapeutic agents have given no indication up to the moment of exerting any curative or prophylactic effect upon the virus disease in experimental animals. Since, however, the evidence points to the fact that the fatalities in epidemic influenza are to a great extent dependent upon bacterial complications, I believe that chemical therapy will be of tremendous value in controlling mortality.

In the presence of a highly virulent virus which of itself would produce a great incidence of pneumonia the outlook would be more problematic. Up to the present, rest, isolation and respiratory comfort have not been supplanted. Probably the most valuable factor in the control of epidemic influenza is increased emphasis on respiratory hygiene, if any such thing exists.

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THE RICKETTSIAL DISEASES, WITH SPECIAL REFERENCE TO THOSE OF IMPORTANCE ALONG THE ATLANTIC SEABOARD*

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GENERAL CONSIDERATIONS

SINCE the beginning of the bacterial era toward the end of the Nineteenth Century, two new and important groups of microscopic pathogens have been discovered, the viruses and the rickettsiae. The rickettsiae, which we are to discuss tonight, have some of the characteristics of ordinary bacteria and some of the attributes of viruses, and there are many bacteriologists who regard them as intermediate between these two forms. In order to understand the diseases which they cause, it is desirable to begin this talk with a brief survey of their life history.

While some of the rickettsial diseases have been known for centuries, the rickettsiae themselves were probably seen first by the brilliant young American bacteriologist, Howard Taylor Ricketts, during his studies of Rocky Mountain spotted fever. After his death from typhus fever, they were named in his honor by da Rocha-Lima, in 1916. Since their discovery the rickettsiae have been intensively studied, and while there are still many gaps in our knowledge concerning them, much has been learned regarding their life history.

Rickettsiae are found all over the world. So far as we know there is no country, civilized or uncivilized, in the temperate and tropical zones in which they do not flourish. Under natural circumstances their hosts are insects and, what is important from the point of view of human disease, many of these are insects which invade and bite man, such as lice, fleas, ticks and mites. However, actual biting is not always necessary, as soiling of the skin by crushing the insects may transmit certain of these diseases. Some rickettsiae are pathogenic both to man and to their insect hosts; some are pathogenic to man but not to the insects which transmit them, while many are harmless to both insects and man.

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Many rickettsiae are able to live and flourish in animals, particularly rodents, but also dogs, rabbits, deer, squirrels, woodchucks, opossums, and many other vertebrates. In invaded animals, as in man, the rickettsiae are carried by insects, notably by fleas and ticks, and in animals also the rickettsial infections may be either clinically inapparent or may result in demonstrable illness. The importance of animal infection lies in the fact that infected animals may serve as reservoirs of rickettsiae during inter-epidemic periods.

Morphologically rickettsiae are smaller than most bacteria. They resemble small cocci or bacilli or may occur in filamentous forms. Variability in form is one of their outstanding characteristics. The bacillary forms average from 0.3 to 0.5 of a micron in length and about 0.3 of a micron in width, but some of them are 6 or 7 times the average length. Rickettsiae are not as readily stained as ordinary bacteria; they decolorize by Gram's method and they stain best with Giemsa's stain or the buffer-formol dyes of Castaneda. Most of them are non-motile and are readily destroyed outside of the body by heat, drying or bactericidal chemicals. They cannot be grown on ordinary culture media but some of them grow quite luxuriantly on media containing fragments of animal tissue containing viable cells. Most of the pathogenic rickettsiae are host-specific, which means that they are always transmitted to man by the same type of insect vector. Furthermore they are more or less tissue-specific and the pathogenic rickettsiae are always intracellular.

Pathology. A brief summary of the pathological lesions common to most rickettsioses is desirable because of its bearing on the clinical picture. The essential damage in practically all rickettsioses is to the blood vessels and the extent of this damage depends upon the character and virulence of the particular rickettsial infection. In the Rocky Mountain spotted fever group, for example, the media of the vessels is mainly affected and, as a consequence, a hemorrhagic skin eruption followed by local skin necrosis, and necrotic lesions of the fingers, toes, ear lobes, scrotum and penis are not infrequent. In typhus fever, in which the intima of the vessels is chiefly involved, there are similar but less severe hemorrhagic and necrotizing lesions. In both these groups involvement of the vessels of the brain explains the severe nervous phenomena which are so common in most rickettsial diseases.

Classification of the rickettsioses in the light of existing knowledge, is difficult for several reasons. The following are the most important:

1. Those who have attempted to classify the rickettsioses have often failed to employ a sufficient number of differential criteria. Not only must the clinical features of the diseases be considered, but the morphology and cultural characteristics of each organism, its immunological reactions, its gross and microscopic pathology, and the effects of its inoculation into animals must also be taken into account.

2. Confusion has been caused by the fact that the same disease has been described by different names, i.e., there are local names which are misleading. Thus the Sao Paulo typhus of Brazil is not typhus fever but Rocky Mountain spotted fever.

3. Confusion has also been caused by the fact that the epidemic and sporadic types of some rickettsial infections show such tremendous differences in mortality that it is hard to believe they were the same disease and also by the fact that, contrasted with bacterial diseases, rickettsial infections show a much wider divergence in symptomatology.

There are three main groups of rickettsial diseases, viz: (1) The typhus fever group, (2) The spotted fever group, and (3) The Japanese River fever group. There are, in addition, three diseases, two of which are undoubtedly rickettsial, which have not yet been satisfactorily classified. One of these is the Australian Q disease; another is Weigl's disease, a purely laboratory infection; and the third is trench fever, which Wolbach does not think is caused by true rickettsiae and which has disappeared since the war of 1914-18. None of these is of importance in this country at present.

There are certain features common to most rickettsiae which may be outlined before discussing the individual diseases in which we are particularly interested. Briefly, these are:

1. Transmission by insect vectors.

2. A primary sore at the point of inoculation in some rickettsioses (Tsutsugamushi, South African tick-bite fever, boutonneuse fever).

3. A clinical course usually beginning suddenly and violently, a hemorrhagic skin eruption, marked involvement of the central nervous system and a high fever which terminates by crisis.

The two groups of rickettsial infection which are important to those of us who practice along the Atlantic Seaboard are the typhus fever group and the Rocky Mountain spotted fever group. These will now be discussed.

The Typhus Fever Group

Clinicians long confused typhus and typhoid fever though works written in the Eighteenth Century, such as Huxham's book on fevers and Langrish's Practice of Medicine, do distinguish between slow, nervous fever, which we call typhoid, and malignant, or putrid malignant fever, which is typhus. It was not until the Nineteenth Century that a clear differentiation, on clinical lines of course, was established by two former students of P.C.A. Louis: Gerhard and Pennock of Philadelphia. We now recognize two forms of the disease, (1) the epidemic and (2) the sporadic or murine type.

The *synonyms* which have been applied to typhus fever are almost innumerable; Murchison lists over ninety of them. Many of them are based on clinical features, such as the skin eruption or the effect on the nervous system, but the most illuminating are those which clearly foreshadow the association of the disease with famine, overcrowding and unsanitary conditions: ship fever, jail fever, camp fever, famine fever.

The *geographical distribution* of typhus fever is world-wide. There is no country either in the Old or the New World which has not, at some time, suffered from the scourge. Under normal conditions there has been a tendency in civilized countries for large epidemics of the disease to disappear. Under abnormal conditions, such as those which accompany the present war on the continent of Europe, the epidemic form of the disease has already developed and is likely to continue until conditions return to normal.

So far as the *etiology* of the disease is concerned the preceding discussion has already indicated the chief *predisposing causes*, viz.: famine and overcrowding, conditions which lower individual resistance and favor the spread of lice from one person to another. It is to be noted that both the head louse and the clothes louse can carry the infection and that the lice themselves are killed by it. The *exciting cause* of the Old World type of epidemic typhus is Rickettsia provaceki, a small, non-filterable, bacterium-like body which is found in the intestinal epithelial cells of the louse. The organism is at times demonstrable in the circulating blood of typhus patients but is present chiefly in the endothelial cells of the blood vessels. It can be successfully grown on media containing tissue, especially the guinea pig tunica-agar-horse-serum medium of Zinsser and his associates. The exciting cause of New World epidemic typhus or tabardillo is the Rickettsia mooseri and sporadic or murine typhus may be

caused by either the Old World or the New World virus.

Symptomatology. The clinical picture of Old World epidemic typhus is indistinguishable from that of tabardillo, the New World type. The period of incubation is apt to be somewhat shorter in the New World type. The average period of incubation of epidemic typhus is nine or ten days. During the period of incubation the patients are usually symptom-free, although a small percentage complain of malaise, slight headache, vertigo and loss of appetite for a day or two before the real onset of the disease. The symptoms of onset are apt to appear with abruptness and violence. There may be a rigor with severe headache and backache, a "bruised sensation" in the limbs, anorexia, fever and at times sweats and great thirst. Nausea is occasional but signs of acute gastrointestinal irritation are usually lacking. Restlessness, tinnitus, vertigo and insomnia, signs of involvement of the central nervous system, are often present from the onset. Deafness is not infrequent. As compared to typhoid fever the symptoms in typhus increase in severity much more rapidly so that at the end of the first week a typhus patient may look like a case of severe typhoid at the end of the second week. Signs of toxemia in the form of persistent, intense headache, confusion or even stupor, muscular twitching and exhaustion are common by the end of the first week. The rash usually appears on the fourth day but may not appear till the seventh. The headache may subside at the beginning of the second week and is often replaced by violent delirium, at times accompanied by suicidal tendencies. Increasing prostration develops as the disease progresses and the patient may become stuporous towards the end of the second week and continue in this condition until the sixteenth or seventeenth day when, if recovery is to take place, sudden improvement occurs with a drop in the temperature and sometimes with a critical sweat or critical diarrhea. In uncomplicated cases the mental condition clears in a few days, the appetite returns and convalescence is quickly established.

The striking things about the physical examination are, (1) the signs of severe toxemia with nervous involvement: the dull, heavy expression, the injected conjunctivae, the dry, brown, tremulous tongue and the muscular twitchings; and (2) the rash. This varies in appearance in different stages. It evolves as a continuous succession of lesions over a period of several days. It is apt to appear first on the anterior axillary folds and the sides of the abdomen and gradually involves the back and ex-

tremities, including the backs of the hands and the dorsa of the feet. *It usually spares the face and neck.* At the outset it is measly looking and consists of irregular, roughly rounded or oval, elevated areas of macular erythema, isolated or grouped, and varying in color from dirty pink to bright red. These disappear on pressure except in the rare cases where the rash is hemorrhagic from the onset. In most cases the rash darkens in shade and does finally become frankly hemorrhagic. It usually persists until the febrile crisis and then fades gradually.

The *fever* in epidemic typhus is usually rather high from the beginning and may reach F. 104° by mouth, even on the first day. It often reaches its maximum by the time the eruption appears toward the end of the first week. At the height of the disease it often ranges between F. 103° and F. 105° in an average case, and in a severe case it may range between F. 104° and F. 107°. The daily variation is usually not more than two degrees and as a rule the increase in the pulse rate parallels the fever. As the temperature falls towards the end of the second week the daily range of temperature becomes greater and as a rule a crisis occurs on the fourteenth to the eighteenth days.

In uncomplicated cases there is little to be made out on physical examination except the signs already described. However, there are certain complications which are fairly frequent, such as acute bronchitis and bronchopneumonia. Before good nursing and care of the mouth were customary, parotitis was a common complication, and in severe epidemics it is usual to have gangrene of the extremities.

The *laboratory findings,* with the exception of the Weil-Felix reaction, can hardly be described as pathognomonic. The urine shows nothing but the ordinary febrile changes. The blood picture varies with the stage of the disease and the severity of the infection. Some writers state that leukopenia is usual until the rash appears, after which there is a leukocytosis with an increase in the polynuclear ratio. While this may be the rule, there are some patients who, from the onset, show leukopenia and a polynuclear ratio as low as 20 per cent.

The so-called *Weil-Felix agglutination reaction* in typhus fever occurs with Proteus OX 19 and may appear as early as the fifth day. In order to confirm the diagnosis of typhus fever an agglutination titer of at least 1 to 50 is necessary. During the period of maximum intensity, which occurs two to three days before the crisis, titers as high as 1 to 2500 may be found, and some agglutination may persist for several

months after the attack is over.

The *diagnosis* of epidemic typhus is not usually difficult except at the beginning of an outbreak, especially if this occurs in a location that has not been visited by the disease for many years so that many physicians may never have seen the disease. The history of infestation with lice, the sudden and violent onset, the character and distribution of the eruption, the marked involvement of the central nervous system and the duration of the fever with termination by crisis constitute a distinctive group of symptoms and signs. Before the eruption appears the disease has been mistaken for meningitis, influenza, smallpox and other severe infectious fevers.

The disease which was formerly confused with typhus fever was *typhoid fever*, but the more gradual onset, the much less profuse skin eruption with its different distribution and character, the positive Widal reaction, and the lack of any increase in leukocytes in typhoid fever should leave no doubt as to the distinction.

In children *measles* may cause confusion, although typhus fever is not preceded by any period of upper respiratory catarrh, and children with typhus fever are very much sicker than children with measles as a rule. There are of course no Koplik's spots in typhus fever and the blood picture is quite different in the two diseases.

In many places more than one type of rickettsial infection may be present at the same period. This is true in the eastern United States, where typhus fever and Rocky Mountain spotted fever both occur. The differentiation between the two will be discussed under Rocky Mountain spotted fever.

Prognosis. There is a great deal of variation in the mortality from epidemic typhus fever in different epidemics and in different regions. In South Africa the average mortality is only about 13 per cent and is much lower in the whites than it is in the negroes. In the New York epidemic of 1893 there was a mortality of 44 per cent. As high as 70 per cent mortality has been reported in some epidemics.

The chief factors influencing mortality are: (1) the mass reduction of resistance by inanition and unhygienic surroundings; (2) age is very important: in children the mortality seldom reaches 5 per cent, after the age of 65 it is generally over 80 per cent; (3) the mortality is generally higher at the beginning than it is at the end of an epidemic; and (4) the presence of complications, particularly bronchopneumonia or peripheral

gangrene adds tremendously to the mortality. Obesity, chronic alcoholism and preëxisting chronic disease also increase the mortality.

Prevention. Inasmuch as the epidemic form of typhus fever is always transmitted by lice, the obvious method of control is to prevent the infestation of human beings by these parasites. In the case of physicians or nurses, the avoidance of louse infestation is a simple problem. Some form of protective covering must be worn. The protective clothing must be composed of some smooth, hard material, of narrow mesh, which is impermeable to lice, and must take the form of a one-piece overall which includes the feet and which can be rendered impenetrable at the wrists and neck. In addition there must be some form of hood which protects the scalp and neck but permits vision.

Inasmuch as epidemic typhus often attacks areas containing congested populations, the problem of wholesale delousing is the most important one in the control of the disease. In the case of troops, systematic bathing and hair cutting with sterilization of clothing can be enforced as a military order. Both lice and rickettsiae are destroyed by moist heat at 70° centigrade for 30 minutes, or dry heat at 55° centigrade for 5 minutes. The wholesale delousing of civilian populations is seldom entirely satisfactory although it has been carried through with some success. Among savage or semi-civilized tribes the problem is even more difficult.

The most satisfactory method of controlling typhus fever in areas where it is at times epidemic is *preventive inoculation.* No doubt the efficiency of this procedure will be tremendously increased by the discoveries of Zinsser and his associates, who have been able to devise methods of growing rickettsiae in large amounts. The method of Weigl, in which a vaccine was produced by using lice as culture media and making a suspension of their centrifugalized and triturated gastrointestinal canals, has been successfully used, but the process is so expensive and time-consuming that the method cannot be used on a large scale.

Murine Typhus

So far as the physicians of this part of the world are concerned murine typhus is much more important than the epidemic type, for while we have not had an outbreak of epidemic typhus in the eastern states for many years, the murine type is constantly present. The name "murine" was given to this form because it has been shown that it is trans-

mitted by rat fleas. Zinsser believed that the murine typhus of New York City might be due to recurrences in adults who had previously had the disease. The researches of Maxcy lend support to the view that the contamination of food by rats and mice may also be a source of the murine type. In New York City this form of typhus has long been known as Brill's disease because the late Nathan Brill was the first to point out its prevalence in this region.

There are a number of points of difference between the epidemic and murine forms of typhus which may be summarized by stating that the murine type is much less severe as a rule. The mortality of the two forms is entirely different. In this country it is probably from 1 to 1½ per cent in murine cases but there are other parts of the world, Tunis, for example, in which the mortality may reach as high as 10 per cent. The period of incubation and the onset of the disease do not differ materially in the murine and epidemic forms, although the onset is often less violent in the murine form. The course of the disease tends to be a little shorter in the murine form and in most patients the fever falls by crisis at the end of the second week. The patient is not so seriously ill in the murine form and the skin eruption is less profuse and much less apt to be hemorrhagic. The Weil-Felix reaction occurs with Proteus OX 19 just as it does in epidemic typhus.

It is obvious that, as the method of transmission of murine typhus is different from the method of transmission of epidemic typhus, the preventive measures are different. In Tunis preventive inoculation has led to a marked reduction in morbidity. In this country the cases are few in number and widely scattered among large masses of people. Preventive inoculation is, therefore, not a practical solution. The only other means of prevention involves rodent extermination and the rat-proofing of buildings, especially those in which food is stored. The extermination of rodents on a large scale is a very expensive procedure and would certainly not be justifiable on the ground of typhus prevention alone. It is possible that if one considered also the losses incurred by farmers and food dealers from rats there might be justification for campaigns against rodents under certain circumstances. Prevention of human contact is not necessary in murine typhus and patients may safely be treated at home.

Treatment. Little need be said regarding the treatment of typhus fever. There is no specific treatment. It is possible that experience may show that some of the modern bactericidal drugs are of value. In brief,

typhus patients are treated symptomatically along the lines that are followed in any febrile infectious disease. Good nursing and good surroundings, free administration of fluids, adequate food supply, and the care of the emunctories constitute the important steps.

The Spotted Fever Group

The only member of the spotted fever group which we need to consider here is Rocky Mountain spotted fever. The name suggests that the disease is limited to the region of the Rocky Mountains but the experience of recent years has shown that it occurs in every part of the country, although there are a few states from which it has not yet been reported.

Rocky Mountain spotted fever may be defined as a specific tick-borne infection due to Rickettsia rickettsi, characterized pathologically by proliferative, degenerative and thrombotic lesions in the peripheral and testicular vessels, and clinically ranging in severity from mild and ambulatory to fulminating and fatal infections, having in the average case a sudden onset with evidences of severe toxemia and a maculopapular rash.

There are two main types of the disease, the Eastern and the Western.* The Eastern type is transmitted by the common dog tick, Dermacentor variabilis, and the Western type is most commonly transmitted by the wood tick, Dermacentor andersoni, occasionally by the rabbit tick, Haemaphysalis leporis-palustris. It is important to point out that the dog tick may be carried by animals other than the dog. It has been found occasionally on horses and cattle, on rabbits, deer, wildcats, foxes, squirrels, opossums, badgers, coyotes, skunks, wolves, asses, hogs, woodchucks, and weasels. The wood tick too may be found on various kinds of deer, on mountain goats, horses, mules, asses, cattle, dogs, badgers, rabbits, woodchucks, prairie dogs, wildcats, hogs, porcupines, and coyotes. The rabbit tick may be found on birds and can be carried by them for considerable distances.

Infection of ticks with the rickettsia of Rocky Mountain spotted fever does not result in the destruction of the insect. On the contrary, the ticks are able to transmit the rickettsiae from one generation to another, and this ability and the fact that various animals can act as hosts

* The Minnesota strain described by Reimann and his associates appears to be a localized mild variety of the Western type.

to the tick account for the keeping alive of the infection during inter-epidemic periods. Only a small percentage of ticks are infected.

Etiology. The chief predisposing cause in the Western type is occupation. Shepherds, cattlemen, hunters and trappers, prospectors, foresters, section hands, road builders and surveyors are especially liable because their work takes them into *wooded country where the ticks are common*. Children are frequently victims of the Eastern type because of their intimate contact with dogs.

The *exciting cause* of Rocky Mountain spotted fever is undoubtedly the organism observed by Ricketts in 1906. Wolbach's classical researches thirteen years later led to the detailed description of the parasite which he named Dermacentroxenus rickettsi. Wolbach showed that the parasite, usually in lancet-shaped forms, can be demonstrated in the vascular lesions of the disease. It has since been rechristened Rickettsia rickettsi and has been grown successfully on tissue cultures by a number of bacteriologists.

Symptomatology. The incubation period of the disease varies somewhat according to the severity of the infection. In the mild cases Parker gives the incubation period at from 3 to 5 days, in the severer ones from 3 to 14 days. During the incubation period a few patients show anorexia, malaise and irritability, but usually the onset of the attack is sudden.

The disease frequently begins with a distinct rigor accompanied by fever and sweating, and commonly with severe headache, backache, and limb aches. Prostration is common from the beginning of the disease and evidences of involvement of the nervous system in the form of photophobia and stupor are also common. Nausea and vomiting occasionally occur at the onset. As in typhus fever, the symptoms usually increase rapidly in intensity and with this rapid increase the nervous symptoms become more marked. Delirium, muscular twitching or even incoördination, restlessness, insomnia, stupor and even coma and convulsions may be present. Examination of the patient at this stage shows a flushed and often apprehensive facies, cyanosis, a palpable spleen, and (according to Parker) frequently a distinctive odor. There may be evidences of meningism and even ankle clonus and the Babinski phenomenon have been noted occasionally. The characteristic rash usually appears from the second to the fourth day but may be delayed until the fifth or sixth day. It is a macular or maculo-papular eruption, at first pink and dis-

appearing on pressure, but gradually becoming darker, bluish rather than pink, and no longer disappearing on pressure. In the milder cases it may come out in crops, in the severe ones it is apt to be hemorrhagic and confluent. It generally appears first on the wrists and ankles, later on the forehead and back, and finally may involve the entire body including the scalp. There is often an enanthem on the mucous membrane of the mouth. After recovery, pigmented areas which become congested on exertion or exposure may remain for some time.

The fever usually lasts for two or three weeks but is not as fixed in duration as the fever of typhus or typhoid fever. In the average case temperatures above F. 103° are rather uncommon. In severe cases the temperature frequently reaches F. 105° early in the disease and in fatal cases may go as high as F. 108°. The maximum temperature usually is reached by the end of the first week and is apt to persist through the second week when a fall by lysis usually begins. Parker notes a difference in the duration of the lysis according to the transmitting tick. Strains transmitted by Dermacentor andersoni occupied 7 to 8 days for the period of lysis, while those transmitted by Dermacentor variabilis only occupy 3 or 4 days.

The ordinary laboratory examinations are not particularly helpful in the diagnosis of the disease. The urine simply shows the usual febrile changes. The blood picture is not characteristic as there may be either a mild leukocytosis, not above 15,000 per cubic millimeter, or a leukopenia. The Weil-Felix reaction in this disease varies but there is usually agglutination of both Proteus OX 19 and Proteus OX 2. In doubtful cases the infection test and the virus neutralization or protection test may be used to substantiate the diagnosis.

Convalescence is apt to be slow even in patients who have had a mild attack, and a complete return to normal may occupy a good many months.

The complications of the disease are those which are apt to occur in almost any infection: pulmonary inflammatory lesions, phlebitis, acute nephritis, and occasionally secondary streptococcic sepsis. The deep gangrenous lesions which may complicate typhus fever are generally absent, although there may be superficial sloughing of the genitalia and the dependent parts of the body in some patients.

Diagnosis. In this region the chief diagnostic problem is the differentiation of Rocky Mountain spotted fever from the murine form of

typhus. There is no marked difference in the onset, though chills are more common in Rocky Mountain spotted fever and headache more prominent in murine typhus. The fever in Rocky Mountain spotted fever lasts longer than that of murine typhus. The distribution of the rash is different in the two diseases, as has already been pointed out. Murine typhus serum agglutinates Proteus OX 19 only, while Rocky Mountain spotted fever serum also agglutinates Proteus OX 2. The Eastern type of Rocky Mountain spotted fever is more common in children while murine typhus is more common in adults. The rat is the only animal reservoir for the virus of murine typhus while many animals may probably serve as reservoirs for the virus of Rocky Mountain spotted fever. The rat flea is the vector of murine typhus while the dog tick is the vector of the Eastern type of Rocky Mountain spotted fever. Murine typhus is usually a disease of cities while Rocky Mountain spotted fever is usually contracted in the country. Murine typhus has a mortality of less than 1 per cent while Rocky Mountain spotted fever has one of about 25 per cent on the average.

Prognosis. A good many writers state that the Western type of the disease is much more fatal than the Eastern type. As a matter of fact the mortality of the Western type shows tremendous local variations. The areas of high case mortality are quite sharply defined and the majority of patients with the Western type suffer from mild to moderately severe attacks. Hampton and Ewbank show that from 1933 to 1937 the mortality in the Pacific states was 19.4 per cent, whereas in the Southern states it was 18.1 per cent. The number of cases which have been reported from the northeast is still so small that one cannot base any conclusion as to mortality upon them.

Prophylaxis. The prevention of the disease in the East, where the disease is carried by the dog tick is somewhat different from prevention in the Western states where it is carried by the wood tick. So far as the Western type is concerned it is to be noted that control of ticks by wholesale extermination of wild animals is hardly a practicable measure. The obvious preventive measure is the protection of the body against the attachment of ticks in all whose occupation takes them into tick-infested areas. As most ticks become attached on the lower leg the protection of legs by high boots, long socks, leggings or puttees is the most important thing. Women tramping in infected areas should wear trousers and should protect their legs just as men do. If the legs are

protected, ticks can only gain access to the body by crawling up clothing, where they may often be seen and removed. If unobserved they may gain access to the arms, especially if the sleeves are rolled up, and to the neck, where they are frequently felt and promptly removed. Persons in tick-infested areas should remove all their garments before retiring for the night and should make a careful inspection of the body. In women it is particularly important that the hairy scalp be inspected. If ticks are found they should never be crushed but should be carefully removed by the fingers or a pair of tweezers by gently pulling on the tick so as to elevate the skin surrounding the area of attachment, and then prying loose the tick from the hypoderm with a hypodermic needle or the point of a scalpel. The small wound thus produced should be touched with a nitrate of silver stick or tincture of iodine. In the East where the disease is transmitted by the dog tick the problem of avoidance is different. Dog owners in districts where ticks are prevalent should be educated to keep their dogs free from ticks.

Individuals who live in known infected areas and whose occupation takes them into wooded regions should be subjected to *prophylactic vaccination*. The United States Public Health Service furnishes a vaccine which is prepared at the Rocky Mountain Laboratory of the National Institute of Health at Hamilton, Montana, and is distributed from this point. At the present time the technique involved in the preparation of this vaccine is difficult, the amount which can be prepared is limited, and the vaccine is therefore expensive. It is to be hoped that with the new methods of cultivation which have been developed it will be possible to produce a vaccine in large quantities by much simpler and less expensive methods. Inasmuch as the protection furnished by the vaccine lasts only one season, annual inoculation is necessary.

Treatment. The treatment of Rocky Mountain spotted fever, like the treatment of typhus fever, is symptomatic and is essentially the same for the two diseases.

Those who have given any study to the subject, are well aware that there are many aspects of the rickettsioses which have been left undiscussed. The question of the relation of rickettsial infection to proteus infection, the details of the serology and immunology, the whole question of the experimental production of these diseases have been barely touched upon. In the time at our disposal it was possible to

emphasize only certain phases of the problem, particularly the practical situation as it applies to this part of the country. If you are desirous of obtaining more information, you can get this from monographs such as the recent work on virus and rickettsial diseases published by the Harvard University Press.*

* *Virus and rickettsial disease: Symposium held at the Harvard School of Public Health.* Cambridge, Mass., Harvard Univ. Press, 1940. 907 pp., illus.

STUDIES ON CHORIOMENINGITIS AND POLIOMYELITIS

Harvey Lecture, October 31, 1940

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CENTRAL nervous system ailments known to be or suspected of being caused by viruses are apparently on the increase and they constitute a puzzling diagnostic problem for the clinician.

For instance, a group of cases characterized by fever with symptoms of meningeal irritation and a clear to slightly turbid, sterile-to-culture spinal fluid showing a lymphocytic cellular response has been considered as a clinical entity under such varied designations as lymphocytic or aseptic or idiopathic meningitis. Laboratory investigators have now split certain etiological entities such as lymphocytic choriomeningitis and pseudolymphocytic choriomeningitis from this group of cases, but there still remains a residue of cases of unknown etiology.

These developments denote progress, yet I fear that the development of an etiological classification has rendered the clinician's problem more complex, since, in the individual case of central nervous infection, an etiological diagnosis is usually not possible on clinical findings alone, but must rest upon laboratory determinations. It is by this fact that I would justify this essentially laboratory presentation of certain aspects of lymphocytic choriomeningitis and of poliomyelitis.

LYMPHOCYTIC CHORIOMENINGITIS

The virus of lymphocytic choriomeningitis was first isolated and described in 1934 at the National Institute of Health.[1] The virus was first isolated with certainty from a human case by Scott and Rivers in 1935 and has subsequently been isolated from widely separated portions of the United States[1, 2, 3, 4, 5, 6, 7, 8] and in England,[9, 10] France[11, 12] and

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Japan[13] and in northern Africa,[14] and there is clinical and serological evidence of its presence in Ireland.[15] There are, moreover, reasons for feeling that the virus is probably world-wide in distribution.

The symptoms as described for etiologically proven cases of choriomeningitis have varied markedly although the viruses isolated therefrom have been immunologically similar with the exception that MacCallum, Findlay and Scott[16] studied two cases which clinically resembled choriomeningitis from which identical strains of virus were isolated. These viruses simulated choriomeningitis in both their clinical and pathological manifestations in experimentally inoculated monkeys and mice, but were found to be immunologically distinct from choriomeningitis and were designated as the virus of pseudochoriomeningitis.

Symptomatology: A sufficiently large number of proven cases of choriomeningitis virus infection have not as yet been observed to assure that all the clinical manifestations of the disease have as yet been identified. However, several clinical types of the disease are now known to exist.

1. *A grippal or non-nervous system type:* Many persons who deny having had any central nervous system ailment whatever have been found to harbor specific virus-neutralizing antibodies in their serums, which suggests the occurrence of a systemic type of infection without central nervous system involvement. This assumption is supported by the fact that susceptible animals, when inoculated with the virus by routes other than directly into the central nervous system, usually develop symptoms without evidence of meningeal or brain involvement; and French investigators[17] have shown the same to be true for human volunteers inoculated subcutaneously with the virus. That such human cases also occur in nature has recently been demonstrated at the National Institute of Health[18] where the first spontaneously acquired case of this systemic type yet reported[18] was observed. The case occurred in a 31 year old man engaged in choriomeningitis research. On March 11, 1940, he developed moderate fever with troublesome pains in his arms and back (Fig. 1). During the next three days his fever increased to 38.8° C. but anorexia, malaise, marked prostration, and lumbar pains so severe as to require codeine were his only complaints. His face was somewhat flushed but otherwise the physical examination was negative. There was no headache, or stiffness of the neck or altered reflexes. A blood count on the fourth day of illness revealed 2900

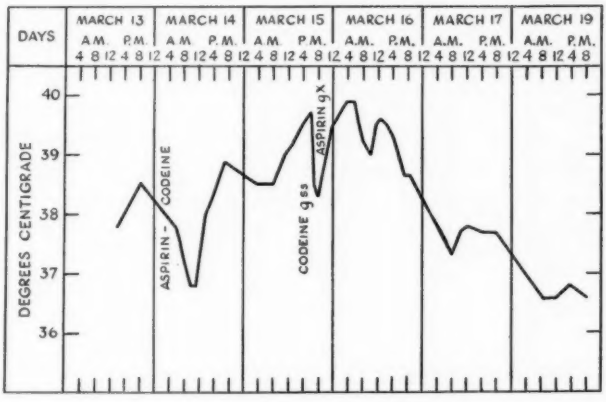

Fig. 1—Temperature course in patient with systemic choriomeningitis virus infection without central nervous system involvement.

white cells of which 45 per cent were polymorphonuclear neutrophiles, 50 per cent lymphocytes, and 5 per cent mononuclear cells. On the fifth day of illness his temperature reached its height, 39.9° C. and there was marked prostration and backache. The next day the fever was lower and his temperature reached normal on the seventh day accompanied by marked amelioration of the pains. Weakness and prostration were marked, however, and persisted for a full week following the return of his temperature to normal. The clinician in charge considered the case to be one of uncomplicated influenza.

There was no indication for a spinal tap and none was done. Blood drawn on the fifth day of illness and inoculated into white mice induced the typical clinical and pathological picture of choriomeningitis and the virus was immunologically identified. Blood drawn in November, 1939 was negative when tested for specific antibodies, while a sample drawn on April 28, 1940 was markedly protective.

This identification of an influenza-like ailment due to the virus of choriomeningitis is of interest in view of the fact that approximately 11 per cent of 2000 sera collected at random from various parts of the United States contained antibodies for this virus, but with rare exceptions the donors when interrogated denied any history of central nervous affection. It is possible, therefore, that a portion of the cases of

"grippe" or "influenza," especially in interepidemic periods may be due to the virus of choriomeningitis.

2. *Meningeal type:* The central nervous system symptoms are often preceded by upper respiratory or influenza-like manifestations which usually improve, to be followed in several days by the sudden appearance of fever with meningeal symptoms such as severe headache, vomiting, stiff neck, and by positive Kernig and Brudzinski signs. The spinal fluid is clear, sterile-to-culture and may contain as many as 3000 cells per cmm., mainly lymphocytes.

3. *Meningo-encephalomyelitic type:* In addition to such purely meningeal symptoms, somnolence, disturbances of deep reflexes, paralysis, and anesthesias have been observed in etiologically established cases. These latter symptoms suggest the presence of encephalomyelitis, for which reason Kreis[19] has justly criticized the designation "choriomeningitis" as being too restrictive in certain cases.

Recovery is usually complete although sequelae probably related to disturbances in the cerebrospinal fluid drainage have been noted in certain cases. Barker and Ford's[5] patient developed persistent symptoms which led to a laminectomy being performed at which time the piarachnoid space was found to be obliterated by fibrous tissue. Other cases have shown a tendency for one to several relapses to occur.

Pathology: No pathological report of an etiologically proven case of choriomeningitis has as yet been made. Viets and Warren[20] have recorded the pathological findings in a patient with acute lymphocytic meningitis who died with convulsions on the fourteenth day of illness in 1934. The etiology in this case was not determined; the choroid plexus was not examined, and the pathological changes reported for the brain were at variance with those usually observed in experimentally inoculated monkeys. We, therefore, do not feel justified in presenting this case as one of probable choriomeningitis infection.

The case reported by Machella, Weinberger, and Lippincott in 1939[21] was, however, clinically suggestive of this ailment and the pathological findings were similar to those observed in experimentally inoculated monkeys. In this case the meninges were infiltrated with lymphocytes and macrophages and were markedly thickened due to connective tissue multiplication with obliteration of the subarachnoid space. The brain substance was in the main not affected. The ventricles were distended, denuded of their ependyma, and there was a narrow

subependymal zone where perivascular lymphocytic infiltration, glial proliferation, and engorgement of vessels and hemorrhages were marked. The choroid plexus was partially necrotic and infiltrated with inflammatory exudate.

Pathology in monkeys: In intracerebrally inoculated monkeys, as described by Lillie,[22] the lesions are characterized by an almost constant, irregular, more or less pronounced lymphocytic infiltration of the choroid plexus, sometimes with an exudate into the ventricles, and by an almost constant, moderate, irregularly distributed infiltration of the pia mater, and by few foci of glial cells and lymphocytic infiltration about the vessels. The cellular infiltration may persist for a long time following the infection. The lungs often present congestion with intracellular edema, serous exudation and perivascular lymphocytic infiltration. Focal interstitial and perivascular accumulations of lymphocytes are frequent in various organs. In this connection it is interesting to note that Armstrong, Wooley, and Onstott[23] and Mendoza[24] have shown the virus to be widely distributed in abundance throughout various organs and tissues of infected monkeys, namely, the adrenals, cerebrum, blood, kidneys, liver, lungs, lymph glands, marrow, heart-muscle, voluntary muscle, pancreas, spinal cord, spinal fluid, spleen, submaxillary glands and testicles, and in amounts not explainable by the presence of virus-containing blood in the vessels. The bile contained no demonstrable virus.

Pathology in mice: Following intracerebral inoculation mice show the same type of meningeal infiltration as noted for monkeys, especially marked at the base of the brain; a lymphocytic infiltration of the choroid plexus with a resulting marked thickening being especially noticeable.

When freshly isolated mouse strains are inoculated subcutaneously or intraperitoneally the central nervous system usually escapes involvement; however, the animals develop marked difficulty of respiration and at autopsy the chest cavity is found filled with a clear virus-containing fluid, the spleen is enlarged and the liver and kidneys often show extreme grades of fatty degeneration. Lesions are entirely lacking when the brain-adapted virus is similarly inoculated.

Host range of the virus: Men, chimpanzees, monkeys, guinea pigs, white rats, cotton rats, rice rats, white mice, gray mice, and dogs are susceptible to the virus. Susceptible birds have not, to date, been found,

although chickens, young chicks, canaries, and pigeons have been tried. These negative results in chickens are of interest in view of the successful cultivation of the virus in the tissue of the developing hen's egg by Bengtson and Wooley.[25] The tissues of the inoculated embryo are rich in virus and many embryos die about the ninth to tenth day, although some of the eggs bring forth living chicks. Such chicks appear rather less active and rather somnolent but usually soon become normal. Laigret and Durand[26] reported the finding of the virus in an uninoculated chick embryo, an extremely interesting result if confirmed.

Personally observed cases: During a period of 17 months five* cases of choriomeningitis were identified in or near the District of Columbia,[7, 27, 28] and one at Lancaster, Pennsylvania.[27]

In five of these cases the virus was recovered from the spinal fluid and in one case where spinal fluid was unattainable the identity of the ailment was confirmed by establishing the absence of specific antibodies early in the disease and their presence subsequent to recovery.

In these six cases, as has been the rule with all reported cases, there was no evidence of contact infection.

This absence of any suggestion of communicability of the disease from person to person raises the question as to the source of the infection.

Virus in mice from infected homes: The knowledge that spontaneous infection with choriomeningitis virus had been detected in mice, monkeys, and dogs naturally suggested the existence of an animal reservoir for the virus from which man becomes infected. With a view to testing this hypothesis the homes of these six patients were investigated as to the presence of vermin, mice, rats, and pets.

Gray mice *(Mus musculus musculus)* were trapped in each home and the virus of choriomeningitis was recovered from a pooled emulsion of livers and spleens of mice captured in *five* of the six homes.

The one failure occurred in connection with the case of a taxicab driver who lived in a poor, isolated abode in nearby Maryland. The patient stated that the home had been overrun with mice and that he had trapped twelve of them from the pantry shortly prior to his illness and that he had also set poison. There was abundant evidence of previous mouse infestation and extensive trapping was undertaken, but only two mice were caught and both proved negative for virus. Thus, while ex-

* Exclusive of two laboratory infections observed during the same period.

posure to mice was established for this patient, we were not able to prove that the mice from the home were actually carrying the virus of choriomeningitis.

One home where infected mice were trapped also kept a dog which was examined but no virus was isolated from its liver or spleen.

Virus studies on mice from seventy-eight homes: More than 400 mice were trapped in homes from various parts of Washington, of which 369 mice survived examination. Of this number 307 were etherized and one kidney and a portion of liver and spleen from each mouse was emulsified in buffered saline (pH 7.6) and 0.03 cc. of the emulsion was inoculated intracerebrally into each of four white mice. When illness resulted, the symptoms and time of death were recorded and a representative sample of forty-six brains from ill white mice were submitted to Surgeon R. D. Lillie, who reported the pathological lesions of choriomeningitis as present in forty-four of them. In two instances the lesions of secondary infection were present.

The final diagnosis of choriomeningitis infection was made, however, by the intracerebral inoculation of four normal mice and of four mice which had been previously immunized to our original strain of choriomeningitis virus.

The inoculation dose of virus employed was 0.03 cc. of a 1:500 suspension of the suspected mouse brain, and in every instance where choriomeningitis virus was finally considered to have been recovered from gray mice, the controls died, while two or more of the immune mice survived. Judged by these criteria choriomeningitis virus was recovered from 65 of a total of 307 gray mice, or approximately one out of every five mice examined was a carrier of the virus. The mice examined were from 78 different homes of which 35 harbored infected mice. Thus it appears that 45 per cent of the mouse infested homes studied were harboring mice infected with choriomeningitis virus. From these 35 infected homes a total of 123 mice were examined of which 65, or 52.8 per cent were carriers of active virus.

The method employed in the above-mentioned studies might be criticized in that white mice were employed as an indicator of infection, since stocks of white mice have on several occasions been found to be spontaneously infected with choriomeningitis virus and it is conceivable that our results were due to the presence of the infection in our white mice rather than in the gray mice which we had trapped.

We feel that this criticism is not valid for the following reasons:

1. The same stock of mice were employed in other virus studies but in no instance was choriomeningitis encountered.

2. It was noteworthy that mice trapped from certain homes were repeatedly found infected while from other households they were consistently negative, a situation which scarcely would have prevailed had we been dealing with a random infection of our stock mice.

3. Gray mice in a number of instances were found to present lesions such as a pleural exudate, fatty liver, and enlarged spleen, which enabled us to predict and later to verify the presence of the virus.

Immunity among trapped gray mice: In order to eliminate all criticism of the employment of white mice as an indicator of the presence of virus, a further test was undertaken. This study was aimed at determining the immunity of gray mice to choriomeningitis, a procedure in which white mice were not employed. Sixty-two gray mice were, therefore, trapped from 22 homes where infected mice had been previously found. These mice were inoculated intracerebrally with 10 to 15 M.L.D. of our original strain of choriomeningitis virus. Of these 62 mice, 41 survived while 21 died, indicating immunity in 66 per cent.

As a control to this group, 47 gray mice trapped in abodes where only non-infected mice had been found, were similarly inoculated, of which only 5, or 10.6 per cent, survived, while 12 white mice employed as additional controls, all died.

The 22 homes from which mice harboring choriomeningitis virus had been trapped and which supplied the 62 mice employed in this immunity test, had supplied 83 mice which were tested for virus, of which 37, or 47 per cent, were found to be carriers. The two methods, therefore, give confirmatory results. The somewhat higher incidence of immunity as compared to active infection (66:47) is what might be expected and suggests that a portion of the mice had probably freed themselves of readily detectable virus but retained their immunity.

Significance of choriomeningitis in mice: The six cases of choriomeningitis in man were widely separated, one in Lancaster, Pennsylvania, two in North West Washington, one in South East, and one in and one adjoining North East Washington. There was no history of contact between any of the cases. Five of the six cases were from homes harboring infected gray mice.

Now if we recall that of 78 homes harboring mice there were 35

which harbored choriomeningitis-infected mice and supplied 5 human cases, while 43 homes harboring non-infected mice supplied only 1 human case, it would appear that these findings are statistically significant, especially when we add to the latter group the large but undetermined proportion of homes which harbored no mice at all and which had no recognized cases of choriomeningitis.

Are mice infected from people or people from mice? There is no recorded instance in which one case had contracted choriomeningitis from another, but on the other hand, a number of cases of the disease have developed among laboratory personnel handling infected mice. The wider extent of the infection in mice, as compared to its recognized human prevalence in the District of Columbia, also suggests that mice, not men, are the reservoir for the infection. The patient noted by Findlay, Alcock, and Stern,[9] who developed choriomeningitis shortly after he had cleaned a shed overrun by mice points in the same direction. Moreover, the tendency for protective antibodies to be relatively most prevalent in the lower economic stratum of society, as noted by Wooley and Armstrong, is hard to explain upon a person-to-person concept of spread, but would be the expected, were mice the source of the infection.

Moreover, the monthly distribution of cases (Table I and Fig. 2) is not inconsistent with this conception. For instance, the Fall peak of cases may be due to the closing of the homes with both mice and men seeking warmer quarters therein. The Spring peak on the other hand, may possibly be related to the birth of litters of infected young during the Spring breeding season.

Choriomeningitis virus in mice: Mice are not readily infected with choriomeningitis through feeding of the virus or by exposure to experimentally inoculated cage mates. It would, therefore, appear improbable that five out of the six cases of choriomeningitis should have in every instance infected the mice in their respective homes especially since in each instance the patient was removed to the hospital during the first days of the illness.

On the other hand, Traub,[29] also Haas[30] have shown that the virus passes readily from the infected mother to her *in utero* young, and that such congenitally infected mice survive birth and may carry the virus for months, while mice infected after birth tend to free themselves rapidly of the virus.

Moreover, while it has been shown that experimentally inoculated

TABLE I

CHORIOMENINGITIS CASES

No.	Color	Age	Sex	Onset		Highest Cell Count Sp. Fluid	Identification-Laboratory		Reported by
				Month	Year		Virus	Neut.	
1	W	19	F	May	1931	3200	−	+	Armstrong & Dickens, P.H.R., June 21, 1935, Vol. 50:831-842
2	W	33	M	Oct.	1931	1520	−	+	Armstrong & Dickens, P.H.R., June 21, 1935, Vol. 50-831-842
3	W	28	M	Mar.	1934	1260	−	+	Armstrong & Dickens, P.H.R., June 21, 1935, Vol. 50:831-842
4	W	3½	F	Nov.	1934	2155	−	+	Collis (Ireland) British Med. J. 1935, *11*: 148[15]
5	W	31	M	Dec.	1934	1700	+	+	Scott, McNair & Rivers, J. Exp. Med. 1936, Vol. 63: 397-414[4]
6	W	33	M	Dec.	1934	720	+	+	Scott, McNair & Rivers, J. Exp. Med. 1936, Vol. 63: 397-414[4]
7	W	20	F	Mar.	1935	409	−	+	Armstrong & Dickens, P.H.R., June 21, 1935, Vol. 50:831-842
8	W	46	M	Oct.	1935	138	+	−	Findlay, Alcock & Stern, Lancet, 1936, Vol. 230: 650-655[9]
9	W	36	M	Oct.	1935	63	+	−	Findlay, Alcock & Stern, Lancet, 1936, Vol. 230: 650-655[9]
10	W	14	F	Oct.	1936	−		+	Dominick, J. A.M.A., 1937, Vol. 109: 247-250
11	W	19	F	Oct.	1936	1380	−	+	Dominick, J. A.M.A., 1937, Vol. 109: 247-250
12	W	26	M	Feb.	1937	2800	+	+	Howard, J. Inf. Dis. 1939, Vol. 64: 66-77[6]
13	W	37	F	Feb.	1936	500	+	−	Barker & Ford, J. A.M.A., 1937, 109: 785-786[5]
14	?	9	?	Apr.	1936	60	+	−	Lesne—cited from Kreis
15	W	11	F	Oct.	1938	101	+	−	MacCallum & Findlay, Lancet, 1939, June 17: 1370[10]
16	C	30	F	Sept.	1939	....			Armstrong, Wallace & Ross, P.H.R. 1940, July 5, 55:1222[27]
17	?	?	F	May	1938	?	+	+	N. Paul Hudson—*Personal communication*[8]

TABLE I—*Continued*

CHORIOMENINGITIS CASES

No.	*Color*	*Age*	*Sex*	*Onset*		*Highest Cell Count Sp. Fluid*	*Identification-Laboratory*		*Reported by*
				Month	*Year*		*Virus*	*Neut.*	
18	W	28	F	Apr.	1938	....	+	−	Lepine & Sautter, Ann. de l'Institut Pasteur, 1938:61:519-526[11]
19	C	23	F	Nov.	1939	1500	+	+	Armstrong & Sweet, P.H.R., 1939, 54:673[7]
20	C	17	M	Nov.	1939	710	−	+	Armstrong & Sweet, P.H.R., 1939, 54:673[7]
21	W	13½	M	Jan.	1939	1330	−	+	Josephine B. Neal: *Personal communication*
22	W	16	F	Dec.	1939	800	+	+	Armstrong, Wallace & Ross, P.H.R. 1940, 55:1222[27]
23	W	26	M	Nov.	1939	2400	+	+	Braun, G. O.: *Personal communication*
24	W	21	F	Feb.	1940	1900	+		H. Saltonstall, Philadelphia: *Personal communication*
25	W	8	M	Sept.	.....	1400			Baird & Rivers, A.J.P.H., 1938, 28:47[36]
26	W	16	M	Sept.	.....	330			Baird & Rivers, A.J.P.H., 1938, 28:47[36]
27	W	33	M	Oct.	.....	63			Baird & Rivers, A.J.P.H., 1938, 28:47[36]
28	W	20	F	Mar.	.....	409			Baird & Rivers, A.J.P.H., 1938, 28:47[36]
29	W	33	M	Feb.	.....	304			Baird & Rivers, A.J.P.H., 1938, 28:47[36]
30	C	15	M	May	.....	1800			Baird & Rivers, A.J.P.H., 1938, 28:47[36]
31	W	24	M	Sept.	1939	1600	+	+	Armstrong: *Unpublished case*[28]
32	W	32	M	Apr.	1939	500	+	+	Armstrong, Wallace & Ross, P.H.R. 1940, 55:1222[27]
33	C	24	M	Oct.	1938	970	+	−	Leichenger, Milzer & Lack, J. A.M.A., 1940: 436[41]

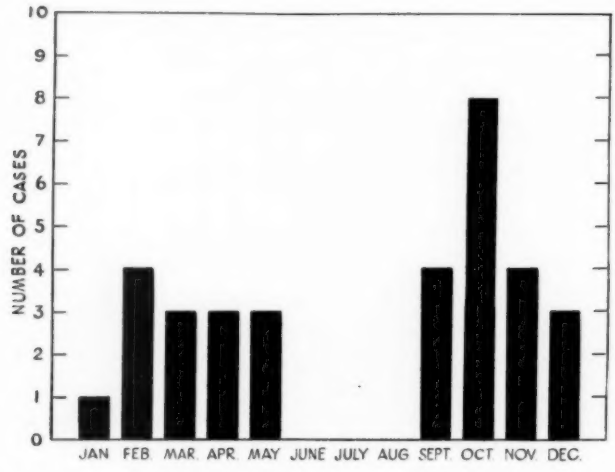

Fig. 2—Monthly distribution of cases of choriomeningitis virus infection.

mice convey the infection to only a portion of their normal cage-mates even after an exposure of one to two months (Kreis,[19] Haas[30]), Haas has, however, shown that congenitally infected mice are much more effective conveyors of infection and may transmit the infection to cage-mates after an exposure as short as one hour.

Moreover, the finding of 52 per cent of the mice trapped in homes harboring infected mice to be active carriers of the virus, in a study extending over several months, points to a persistent type of infection such as follows the congenital method of spread rather than toward an infection of mice from man.

Method of spread of infection between mice and man: The presence of the virus in the blood stream and the ready transmission of the systemic type of the infection by subcutaneous inoculations suggest the possibility of an insect transmission.

We have, moreover, succeeded in two instances out of several trials in transferring the infection by means of approximately 100 lice taken from an infected monkey and directly transferred to a normal one.

Attempts to transfer the infection by bedbugs, rat and mice fleas, and a bloodsucking mite have, however, uniformly failed. The virus could be detected in each species when the engorged arthropods were

emulsified and inoculated into normal mice within one hour of the infective feeding, but not after longer intervals. Attempts to convey the infection through biting were entirely negative.

Coggeshall[31] reported the transmission of choriomeningitis to one guinea pig through the bites of seven *Aedes aegypti* mosquitoes made five days after feeding upon an infected guinea pig. Shaughnessy and Milzer[32] succeeded also in infecting Rocky Mountain wood ticks by feeding them on infected animals and demonstrated that the infection could pass through the complete life cycle of the host. Controlled biting experiments were entirely negative but, when infected nymphs were put in the cage with normal guinea pigs, infection occurred. It is probable that these observations have little if any bearing upon the spread of choriomeningitis in nature, for established cases have been noted throughout the winter in latitudes where mosquitoes and ticks are scarce or absent during this period; while in June, July and August, the months when mosquitoes and ticks are prevalent in the northern hemisphere, there have been no proven cases reported (Fig. 2).

The seasonal distribution of cases and the respiratory symptoms so commonly noted in choriomeningitis infections, moreover, suggest a respiratory route of infection. The case of a laboratory worker reported by Lepine, who developed symptoms six days after splashing infectious material into her eye is, moreover, consistent with this route of infection as is the patient reported by Findlay[9] who developed the disease after cleaning a mouse infested shed.

The virus escapes from infected mice by way of the nasal secretions, urine, and feces, and it is conceivable that dust plays a part in the transfer of the infection to man, although it is possible that contaminated food may play a part; it appears, however, that experimental animals are more susceptible to freshly isolated strains given intranasally than they are by feeding. The investigations of Shaughnessy and Zichis[33] on guinea pigs suggest the possibility that the virus may also be able to pass through the unbroken skin.

Why are there not more human cases? In view of the extent of the mouse infestation and infection in the District of Columbia, it is natural to enquire why more human cases of choriomeningitis have not become apparent. As stated above, the recognition of the disease has been practically confined to the central nervous system types of the ailment, while the systemic type of the infection has probably escaped identification.

The fact that approximately 11 per cent of 2000 sera collected at random possessed neutralizing antibodies for choriomeningitis virus, while the donors largely deny a history of central nervous system disease at any time, points toward an unrecognized infection with the virus as being quite common.

It, therefore, seems probable that choriomeningitis virus infection is more common than is indicated by the occasionally occurring meningeal type of the infection. The reason more cases of this latter type do not occur is probably attributable to the efficient barrier which tends to protect the central nervous system against various infections.

Special considerations: The wide range of species susceptible to experimental infection with choriomeningitis along with the finding of naturally infected mice, monkeys, and dogs gives the virus an especial importance for those engaged in animal experimentation with other viruses. For instance, Dalldorf and Douglass[34] recovered choriomeningitis virus from four different dog spleens and found suggestive evidence of its presence in several others. Needless to state, the unexpected intrusion of this virus led to some temporary confusion in their canine distemper investigations.

A commercial manufacturer, likewise, has encountered choriomeningitis in the preparation of canine distemper tissue vaccine and Mollaret[35] has raised the question as to whether this virus may not have been responsible for some of the meningeal reactions observed in the early attempts to vaccinate against yellow fever by means of mouse tissue vaccine.

Diagnosis: Choriomeningitis should be considered whenever a lymphocytic type of meningitis of unknown etiology is encountered, whether or not it be associated with symptoms of encephalitis and encephalomyelitis. The case reported by MacCallum and Findlay[10] further shows that choriomeningitis may occasionally simulate poliomyelitis. These authors isolated choriomeningitis virus from the spinal fluid as well as repeatedly from the nasal secretions of this case. Furthermore, this infection must be considered in cases of sporadic "grippe-like" infections.

There are at present, however, no characteristic symptoms by which the clinician can with certainty diagnose this infection, although, the finding of a clear spinal fluid with a cell count above 1200, mainly lymphocytes, points, as Baird and Rivers[36] have stated and as our experience indicates, toward lymphocytic choriomeningitis. The diagnosis rests ul-

timately, however, upon either the isolation of the virus or the demonstration of a developing immunity.

The virus is most readily recovered from spinal fluid or blood drawn preferably at or prior to the height of the attack, and less regularly in later drawn samples. The virus has also been occasionally isolated from the patient's urine and nasal discharges. The inoculation of susceptible animals should be promptly carried out, or when delay is unavoidable the material should be promptly chilled and held near freezing.

A study of the serum for neutralizing or complement-fixing antibodies may also yield diagnostic evidence. Blood for such tests should be drawn with sterile precautions and handled without the addition of anti-coagulants or preservatives of any kind. This statement is prompted by the fact that we receive at the National Institute of Health many samples mailed from various parts of the United States which contain anti-coagulants, glycerine, or other preservatives. It is also surprising how frequently blood is mailed in cotton stoppered containers from which the serum, of course, uniformly escapes.

Virus-neutralizing antibodies are usually not demonstrable in the blood before 6 to 10 weeks following the onset of symptoms, but in our experience, they invariably appear in established cases. Howard,[37] however, reported two cases in which demonstrable virus-neutralizing antibodies failed to appear following the attack. Once established, neutralizing antibodies tend to persist for months or even years. Baird and Rivers[36] report the case of a child 8 years of age in which the antibodies disappeared after 8 months. We have, however, examined patients as much as 3½ years after the attack and found the antibodies undiminished.

It is desirable that blood be drawn early in suspected cases and again some 6 to 10 weeks following the attack. Both samples should then be tested for antibodies when a definite increase in the later drawn as compared to the earlier drawn specimen may be considered of diagnostic significance.

Complement fixation, as carried out by Lepine, Mollaret and Sautter[38] and by Smadel, Baird and Wall[39] is also a valuable diagnostic procedure. Complement fixing antibodies make their appearance earlier and tend to be less persistent than the slower developing neutralizing antibodies.

Treatment: There is no specific treatment of proven value known. The favorable experimental results secured in mice with prontosil by

Rosenthal, Wooley and Bauer[40] have not been consistent and when effective were apparently dependent upon early administration and more nearly approach prophylaxis than they do treatment.

Leichenger, Milzer and Lack[41] feel that sulfanilamide was effective in one patient observed by them in spite of the fact that the patient suffered four distinct relapses and the illness persisted for 4 months.

Spinal drainage is the one measure that frequently has afforded relief from the severe headache and vomiting. Cellular changes in the spinal fluid may persist for a considerable period following the disappearance of acute symptoms and accumulating instances where one or more relapses occur indicate that there is danger in discharging the patient to full activity before the spinal fluid has returned to normal.

Prevention: There are many details of the exact manner of spread for the virus yet to be determined; the findings reported do, however, suggest that prevention would be served by the construction of homes with a view to rendering them mouse proof and by reducing or eliminating mouse infestation from quarters frequented by people.

Poliomyelitis

Poliomyelitis is a disease that has been much studied but the investigations have, to date, singularly failed to answer definitely many fundamental epidemiological considerations relating to this disease, such as the method of spread of the virus, and the portal of its entry to the central nervous system. A noteworthy recently established fact is that the virus of poliomyelitis may exist in the intestinal tract of man from which it escapes, in readily detectable amounts, along with the dejecta. The significance of this fact is, however, a matter of controversy and any attempt to present the *pros* and *cons* of this discussion would be time-consuming and without hope of reaching a definite or convincing conclusion at this time. I shall, therefore, forego consideration of the controversy raised by this recent development and proceed to a consideration of the cotton rat and white mouse in poliomyelitis research.

In so far as availability, cost and such general considerations are concerned the cotton rat and white mouse are admirable laboratory animals. Their suitability for poliomyelitis research is, however, dependent upon the degree and uniformity of susceptibility, the incubation period, and the definiteness of the symptoms. It is these factors which I wish to consider.

Susceptibility to new strains: The susceptibility of the cotton rats to new strains is apparently low; for instance, in 1937 and again in 1938 we were able to transmit a monkey-adapted strain of poliomyelitis from Lansing, Michigan, to one of two and one of eleven cotton rats, respectively, after an incubation period of 29 days in each instance, but attempts at further passage failed. In 1939 one of four inoculated rats developed symptoms and from this rodent the strain has been successfully carried through fifty-five successive transfers and after seven generations was successfully conveyed to white mice.

During 1939 we had one of four cotton rats develop symptoms following inoculation with a strain of virus from Niagara Falls after an incubation period of 41 days. We also produced symptoms in one of several rodents with a strain of virus from Detroit and succeeded in carrying it through three generations. Further attempts at transfer failed in both instances, as did attempts to convey six additional strains to cotton rats.

Other investigators have attempted to convey many strains of poliomyelitis to cotton rats but with few successes. For instance, Jungeblut and Sanders[42] succeeded, three times, in passing a virus to cotton rats, employing the monkey-adapted S.K. poliomyelitis strain, which was originally of fecal origin. After passage in cotton rats the virus was found to be pathogenic for white mice, in which species it showed extreme potency and a remarkable capacity to pass the central nervous system barrier, but with mouse passage it tended to lose its pathogenicity for monkeys. This virus differs markedly from the mouse-adapted Lansing strain of virus, which was of nervous system origin, and it is conceivable that neuro and fecal strains may behave differently. The authors kindly supplied me with their strain of virus and I regret that I have not been able to work with it, due to the stress of more urgent but not necessarily more important duties. Therefore, I am not able to express an authoritative opinion on the authors' contention that their murine virus is immunologically one of poliomyelitis. The most convincing evidence set forth by the authors in support of this contention is, perhaps, the fact that the pseudoglobulin concentrate from an R.M.V. antipoliomyelitis horse serum "neutralized" their murine virus in high concentrations. It is noted, however, that an R.M.V. antipoliomyelitis serum from a convalescent monkey gave no neutralization against the same strain of virus. The authors explain this discrepancy in behavior of the two anti-R.M.V.

sera as due to "The enormous potency of the hyperimmune horse serum breaking down immunological strain differences." The authors, however, also mention in passing that diphtheria antitoxin (pseudoglobulin) in several tests also inactivated large doses of murine virus.

It is difficult to harmonize these results on the basis of specific neutralization and I am wondering if the authors have considered the possibility that their concentrated sera may have contained a preservative. I make this inquiry because a preservative is required, by Federal regulation, to be added to serum concentrates if prepared for human use and intended for inter-State sale. Moreover, many producers follow Federal requirements in preparing sera for intra-State use. The presence of a preservative such as merthiolate or phenol, acting for 1½ hours at 37° C. and over night in the ice box prior to inoculation, would have opportunity to destroy a portion of the virus; the result would simulate a true neutralization and supply a ready explanation for the odd results secured by the authors. Should this possible explanation be the correct one, the remaining evidence of immunological relationship with poliomyelitis would be so slight as to cause one to doubt whether the murine virus was related to poliomyelitis virus at all.

A personal communication has recently been received from another investigator who claims to have transferred the P.M.V. strain of poliomyelitis to cotton rats. He kindly sent me some of this virus strain and when inoculated into cotton rats it produced symptoms similar to those caused by the Lansing strain, but it has not been further identified at the National Institute of Health.

The evidence thus indicates that the cotton rat is a far less satisfactory animal for the primary isolation of poliomyelitis strains than is the monkey.

Susceptibility to Lansing strain: Cotton rats and white mice appear to be quite susceptible to the adapted Lansing strain. The incubation period in the former is usually 3 to 8 days, while in white mice symptoms become apparent usually in 2 to 10 days following inoculation, but the interval has been observed to be as short as 24 hours and as long as 93 days. In both these rodent species the symptoms are very distinct, paralysis of one or more legs being usually first observed, while paralysis of the neck, back, and tongue have been seen. Death occasioned by respiratory paralysis usually takes place within 12 to 48 hours of the first recognized symptoms. White mice almost uniformly succumb when .03 cc.

of a suspension of infected mouse brain in a dilution up to 1:500 is employed and a portion of the inoculated mice will develop symptoms with dilutions as high as 1:10,000. Occasionally an animal recovers after having developed symptoms. In such instances of recovery muscle atrophy and deformities usually develop.

Route of inoculation: The only successful route of inoculation for rodents employing the Lansing strain of virus consists in the direct inoculation of the central nervous system. Intranasal, intraocular, subcutaneous, intraperitoneal inoculations, as well as feeding, have all failed to induce infection. Unless these negative results can be overcome it is difficult to see how these rodents can contribute much toward elucidating the natural route of infection or transit of the virus in man.

Immunity: Mice and cotton rats which have recovered from paralytic attacks induced by the Lansing strain are solidly immune to intracerebral inoculation with the virus.

Humoral immunity: When Lansing virus-infected mouse brains are inoculated under the skin of mice or cotton rats they develop potent humoral antibodies readily demonstrable by the serum-virus protection test in mice or cotton rats. Such antibodies exert a slight protective action against intracerebrally inoculated minimal infective doses of virus (Table II). It is conceivable, however, that the protective action may be due to the artificial method of inoculation since the needle in some instances probably produces some bleeding at the inoculation, where the plasma coming into direct contact with the virus would, if immune, tend to prevent infection. The artificial method of inoculation necessary to bring about infection in mice, therefore, tends to cast doubt upon the significance of the degree of protection afforded subcutaneously immunized mice when minimal infective doses of virus are employed.

Humoral immunity in the population: Approximately 300 human sera from various sources have to date been submitted to the serum-virus neutralization test in white mice, employing the mouse-adapted Lansing strain of virus. The test is rapid, requires but .45 cc. of serum, and the results are usually definite, easily read, and readily repeatable (Table III).

This group of 300 tested human sera is larger than any series yet reported by a single laboratory employing monkeys; however, we consider that we have just begun. No detailed analysis of our results will, therefore, be attempted at this time. In general, the results secured to

TABLE II

INFLUENCE OF SUBCUTANEOUS INOCULATION UPON LATER INTRACEREBRAL INOCULATION

1940. *Experiment 1109.* *Immune Status of Mice*	*Virus subcutaneously 7-12-40*		*Virus dilution intracerebrally .03cc.*	*No. mice intracerebrally inoculated*	*Deaths by Days Following Inoculation*																				*No. mice surviving*	*Per cent of mice dying*
Immune Status of Mice	6/27	7/3			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21		
Immunized	+	+	1/500	30	*3			10	2		1		2						1	3		3				5	81.5
Controls	−	−	1/500	35	*2	2		13	1			1	2		3	1	4	2	1							3	90.9
Immunized	+	+	1/2500	30		1	1	3		2					1	2	1								1	18	40.0
Controls	−	−	1/2500	33	*1			8	1			1			3		2			1		2	1			13	59.4

*Indicates deaths: Excluded as due to Trauma. Immunized and Control Mice bled July 11, 1940.

TABLE III.

SERUM-VIRUS PROTECTION TEST WITH WHITE MICE

PROTOCOL

*Serum	*Virus Dilution inoculating 4 mice*	*Deaths by Days Following Serum-Virus Inoculation*																			*Survived*	
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21		
P-131	1/10																						4	
	1/20																						4	Immune
	1/40																						4	
P-132	1/10						1	1			1			1									0	
	1/20							2						2									0	Not
	1/40							1		1													2	Immune
P-133	1/10			1						1				2									0	
Negative	1/20		1					1				1					1						0	Not
Control	1/40							1		1			1							1			0	Immune
P-134	1/10																						4	
	1/20																					1	3	Immune
	1/40																						4	
P-135	1/10																						4	
	1/20																						4	Immune
	1/40																						4	
P-136	1/10																						4	
Lennett+	1/20																						4	Immune
Control	1/40																						4	
P-137	1/10							2	1	1													0	Not
	1/20					1				1	1												1	Immune
	1/40										1	1		1				1					0	

* .1cc. undulated + .15cc. various dilutions of virus held for 1 hour at room temperature. .03cc. of mixture inoculated intracerebrally.

date are in agreement with those secured in monkeys. For instance, 65 per cent of the sera possessed definite immunity, 6.5 per cent partial immunity, and 28.5 per cent no immunity; the percentage of immune sera increased with age of the donors, and children living in institutions tended to show a higher proportion with immunity than was the case with the same age group living in urban dwellings.

The test is so inexpensive and can be so rapidly performed that it is now possible to study adequately humoral immunity in groups and geographical units of the population and by repeated tests to follow immunity development in individuals; and in this way to elucidate, it is hoped, the epidemiology of the disease, at least, in so far as one strain of virus is concerned.

Chemotherapeutic studies: Cotton rats and white mice along with the Lansing strain of virus are also being utilized in the search for curative agents in poliomyelitis and they will permit studies to an extent practically impossible with the monkey.

Is the Lansing strain exceptional or peculiar? In view of the various studies now being pursued with the Lansing strain of virus it seems appropriate to inquire if this strain of virus is exceptional or peculiar. The virus originated from what was clinically considered to be a typical case of fatal bulbar poliomyelitis. The clinical and pathological picture produced in monkeys with this strain of virus both before and after its transmission to cotton rats and white mice is identical and confirms the opinion that the Lansing strain is one of typical poliomyelitis. The finding of virus-neutralizing antibodies in 71.5 per cent of approximately 300 human sera from various localities of the United States further indicates that the Lansing strain of virus is immunologically a commonly occurring one. The finding that four out of seven antisera collected from monkeys convalescent from various strains of poliomyelitis protected mice against the Lansing strain of poliomyelitis virus points in the same direction.

The sera tested which gave positive results were as follows:

		Results
1.	From Lennette (P.M.V.)	+
2.	From Niagara Falls, 1938	+
*3.	From S. D. Kramer, Michigan (Rhesus 91) . .	+
*4.	From S. D. Kramer, Michigan (Rhesus 83) . .	+
5.	From Aycock, Boston	−
6.	From Charleston, S. C., 1939	−
†7.	From S. D. Kramer, Michigan (Rhesus 41) . .	−

The failure of three convalescent monkey sera to show protection against the Lansing strain appears to be in agreement with strain difference indicated by the work of Burnet and Macnamara,[43] Weyer,[44] Paul and Trask,[45] Kessel and co-workers,[46] and others. This apparent confirmation, however, rests on an assumption since we have not demonstrated that the three sera, which lacked apparent neutralizing antibodies for the Lansing strain, actually possessed antibodies at all, since the homologous viruses had not been adapted to mice and we did not feel justified in sacrificing monkeys for the purpose.

* A communication from S. D. Kramer subsequent to delivery of this paper reveals that sera 3 and 4 were from monkeys immunized against the Lansing strain of virus.
† Animal number 7 died of tuberculosis.

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PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETINGS

JANUARY 2—*The New York Academy of Medicine. Annual Meeting.* Executive session—a] Reading of the Minutes; b] Presentation of certificates of Fellowship. ¶Presentation of annual reports (by title only); The council, the trustees, the treasurer, committees. ¶Presidential address: "What is The New York Academy of Medicine?" Malcolm Goodridge. ¶Scientific program: Newer knowledge of the steroid hormones—a] Chemical, physiological and clinical aspects of the estrogens, Ephraim Shorr, Assistant Professor of Medicine, Cornell University Medical College; b] Chemical, physiological and clinical aspects of the androgens, John Eager Howard, Associate in Medicine, Johns Hopkins University, School of Medicine; c] Chemical, physiological and clinical aspects of progesterone, William M. Allen, Professor of Obstetrics and Gynecology, Washington University, School of Medicine. ¶Report on election of trustee and fellows.

JANUARY 16—*The Harvey Society in affiliation with The New York Academy of Medicine.* The fourth Harvey lecture, "Adjustments of Nerve Endings," Dr. Carl C. Speidel, Professor of Anatomy, University of Virginia.

SECTION MEETINGS

JANUARY 3—*Surgery.* Reading of the minutes. ¶Presentation of cases—a] Staphylococcus aureus septicemia; osteomyelitis of femur and humerus; suppurative pericarditis. Recovery, Francis McG. Donehue; Discussion, Hugh Chaplin; b] Staphylococcus aureus septicemia; osteomyelitis of ilium; suppurative pericarditis. Recovery, A. J. Abeloff; Discussion, Frank L. Meleney; c] Osteomyelitis of femur, humerus and ilium; retroperitoneal abscess. Recovery, Frank B. Berry. ¶Papers of the evening; a] The use of sulfanilamide locally in peritoneal infections, James E. Thompson; Discussion, R. S. Mueller (by invitation); b] Modern treatment of war wounds, Charles Bove (by invitation); Discussion, John A. McCreery. ¶General discussion.

JANUARY 7—*Dermatology and Syphilology.* Presentation of cases—a] Vanderbilt Clinic; b] Miscellaneous cases. ¶Discussion of cases. ¶Executive session.

JANUARY 7—*Combined Meeting The New York Neurological Society and the Section of Neurology and Psychiatry.* Reading of the minutes. ¶Papers of the evening—a] Neuropsychiatric disturbances in Addison's disease, George L. Engel (by invitation), Sidney G. Margoline (by invitation); Discussion, Israel Wechsler, Norman Jolliffe (by invitation); b] The narcoleptic-cataleptic syndrome. An excessive and dissociated reaction of the sleep-regulatory mechanism, and its accompanying mental states, Samuel Brock, Benjamin Wiesel (by invitation); c] Oliver Wendell Holmes—A Precursor of Freud, C. P. Oberndorf; Discussion, Tracy J. Putnam, John Alfred Parsons Millett (by

invitation), Foster Kennedy. ¶General discussion. ¶Executive session.

JANUARY 8—*Combined Meeting Section of Historical and Cultural Medicine and the New York Physical Therapy Society.* Executive session—a] Reading of the minutes; b] Appointment of nominating committee. ¶Papers of the evening—a] August Kekulé, first of the modern chemists, Herman Goodman; Discussion, Victor Robinson (by invitation), Chester Myers; b] Celebrated figures in electrotherapy, Richard Kovacs; Discussion, Madge C. L. McGuinness, Iago Galdston.

JANUARY 9—*Pediatrics.* Reading of the minutes. ¶Papers of the evening—a] Deafness in little children. Early detection, management and treatment. Demonstration by children of the New York League for the Hard of Hearing, Edmund Prince Fowler; Discussion, J. Taylor Howell; b] Virus diseases of the eye in infancy, Gordon M. Bruce; Discussion, M. Sanders (by invitation); c] Newer conceptions of ophthalmia neonatorum, J. Vincent Flack (by invitation); Discussion, Eleanor L. Adler (by invitation).

JANUARY 15—*Genito - Urinary Surgery.* Reading of the minutes. ¶Papers of the evening, *Commemorating the Twentieth Anniversary of the Department of Urology (James Buchanan Brady Foundation) of the New York Hospital:* a] The adequate treatment of prostatic disease with special reference to pathology, Roy B. Henline; b] Management of carcinoma of renal pelvis with report of an interesting case, Thomas J. Kirwin; c] The role of the Brady Foundation in urology at the New York Hospital, Oswald S. Lowsley; d] Reminiscences of early experiences in urology in New York City, Colin L. Begg. ¶General discussion. ¶Executive session.

JANUARY 15—*Otolaryngology.* Reading of the minutes. ¶Presentation of cases—a] Pneumococcus Type III—mastoiditis and meningitis; operation; recovery, Alvin M. Street (by invitation); b] Frontal sinusitis; osteomyelitis and meninginitis; operation; recovery, J. Swift Hanley; c] Meningitis; labyrinthitis; operation; recovery, Jackson A. Seward; d] 1. Total laryngectomy; 2. Foreign body in maxillary sinus, Eugene Moyle; e] Specimen of healed petrositis, J. Winston Fowlkes. ¶Paper of the evening, Cancer of the paranasal sinuses, William L. Watson; Discussion, Douglas Quick. ¶General discussion.

JANUARY 20—*Ophthalmology.* Exhibits 7:00 to 8:30 o'clock (by invitation); a] A device for doing light threshold studies, Jacob B. Feldman, Philadelphia; b] A demonstration of some effects of aniseikonia, Hermann M. Burian, Hanover, New Hampshire; c] The central visual field (angioscotometry), John M. Evans, George Graham, Charles Rosenthal; d] Comparative micranatomy of the anterior chamber angle in mammalia, Manual Uribe Troncoso; e] Demonstration of contact glass technique. ¶Reading of the minutes. ¶Papers of the evening, Clinical Evaluation of Recent Advances in Examination and Functional Testing of the Eyes—a] Orthoptics, Maynard C. Wheeler; b] Gonioscopy, John M. McLean, Baltimore (by invitation); Discussion, Manuel Uribe Troncoso (by invitaton); c] Aniseikonia, Hermann M. Burian, Hanover, New Hampshire (by invitation); d] Light threshold studies, Jacob B. Feldman, Philadelphia (by invitation); e] Angioscotometry, John M. Evans (by invitation).

JANUARY 21—*Medicine.* Reading of the minutes. ¶Papers of the evening—a] Avitaminosis from the point of view of internal medicine, Thomas T. Mackie; b] Avitaminosis from the point of view of neurology and psychiatry, Norman Jolliffe; Discussors, William C. MacTavish, Gilbert Dalldorf. ¶General discussion. ¶Executive session.

JANUARY—*Orthopedic Surgery.* There was no meeting of the Section of Orthopedic Surgery in January because of the annual meeting of the American Academy of Orthopædic Surgeons in New Orleans, January 12-16.

JANUARY 28—*Obstetrics and Gynecology.* Reading of the minutes. ¶ Papers of the evening: *(Program by Sloan Hospital for Women)* "Difficult Labors"—a] Introduction, B. P. Watson; b] Prognosis of labor in the prenatal patient, J. W. Draper (by invitation); c] Problems of first stage, W. E. Caldwell; d] Difficulties due to occiput-posterior position, D. A. D'Esopo (by invitation); e] The android pelvis as a cause of difficulty, H. C. Moloy (by invitation); f] The lessons infant autopsies teach us regarding breech delivery, J. C. Boyd (by invitation); g] Trial labor—what is it? B. P. Watson.

AFFILIATED SOCIETIES

JANUARY 20—*New York Roentgen Society in affiliation with The New York Academy of Medicine.* Symposium on Radition in Operable Breast Cancer, Douglas Quick. ¶ Discussion, Edith Quimby (by invitation), Frank E. Adair, William Harris, Alfred F. Hocker (by invitation), Milton Friedman. ¶Executive session.

JANUARY 23—*New York Pathological Society in affiliation with The New York Academy of Medicine.* Papers of the evening—a] The morphogenesis and significance of "intercapillary glomerulosclerosis" (15 minutes), Arthur C. Allen (by invitation), Mount Sinai Hospital; b] Morphological analysis of tuberculous lesions in adults (40 minutes), Kornel Terplan (by invitation), Buffalo General Hospital; discussion was opened by J. Burns Amberson and Eugene L. Opie. ¶ Executive session.

DEATHS OF FELLOWS

BEGG, COLIN LUKE: 118 East 54 Street, New York City; born in Glasgow, Scotland, December 9, 1873; died in New York City, January 15, 1941; received the degree of A.B. from Queen's University, Canada, in 1895 and graduated in medicine from the University of Toronto in 1899; elected a Fellow of the Academy May 24, 1906.

Dr. Begg served as professor of urology at the New York Post-Graduate School of Medicine and Hospital and was consulting urologist to the New York Skin and Cancer Hospital, surgeon to the New York Hospital Out-Patient Department, and a member of the staff of the Department of Urology, the James B. Brady Foundation at that hospital.

Dr. Begg was a diplomate of the American Board of Urology and one of its founders, a Fellow of the American Medical Association, a member of the American Neisserian Medical Society and the County and State Medical Societies.

DAVIS, ACHILLES EDWARD: 40 East 61 Street, New York City; born in Harrodsburg, Kentucky, February 18, 1866; died in Scarsdale, New York, January 17, 1941; received the degree of B.A. in 1886 and M.A. in 1889 from the Central University of Kentucky; graduated in medicine from the University of Louisville in 1889; elected a Fellow of the Academy February 2, 1899.

Dr. Davis was consultant on diseases of the eye to the New York Post-Graduate Medical School and Hospital, and consulting ophthalmic surgeon to the Manhattan State

Hospital at Central Islip, Long Island, since 1889, the United Hospital at Port Chester, New York, since 1911, and the Ossining Hospital at Ossining, New York, since 1913. He was a Fellow of the American College of Surgeons, the American Medical Association, and a member of the Pacific Coast Oto-Ophthalmological Society, the American Academy of Ophthalmology and Otolaryngology, the American Ophthalmological Society, the Association for Research in Ophthalmology, Inc., and the County and State Medical Societies.

Especially known for his work in cataract cases, Dr. Davis wrote many papers on that and allied subjects. Among his publications were: "The Refraction of the Eye," 1900; "Handbook of the Anatomy and the Diseases of the Eye and Ear," (in collaboration) 1904; "Eye, Ear, Nose and Throat Nursing," (in collaboration) 1905; and "Medical Treatment of Cataract," 1937. He also wrote the section on refraction in the "American Encyclopedia of Ophthalmology," 1919.

Dr. Davis was a member of the Officers' Reserve Corps and served as Captain in the United States Army Medical Corps during the World War.

ESTES, WILLIAM LAWRENCE, SR.: Bethlehem, Pennsylvania; born in Brownsville, Tennessee, November 28, 1855; died in Bethlehem, Pennsylvania, October 20, 1940; graduated in medicine from the University of Virginia in 1877 and from University Medical College of New York in 1878; received the honorary degree of M.A. from Bethel College, Kentucky, in 1893; elected a Fellow of the Academy December 6, 1906.

Dr. Estes was emeritus surgeon-in-chief of the St. Luke's Hospital, Bethlehem; lecturer on physiology and hygiene at the Lehigh University, 1883-1923; and chief surgeon to the Lehigh Valley Railroad, 1888-1904. He was a Fellow of the International Surgical Association, the American Surgical Association, the American College of Surgeons, an Associate Fellow of the College of Physicians, an Honorary Member of the Association of Industrial Surgeons of America, a member of the Pennsylvania State Medical Society and the American Medical Association.

NEAL, PHILEMON HAWKINS: 145 East 74th Street. New York City; born in South Boston, Virginia, October 21, 1896; died in New York City, January 21, 1941; graduated in medicine from the Medical College of Virginia in 1923; elected a Fellow of the Academy April 5, 1934.

Dr. Neal was assistant surgeon to the New York Eye and Ear Infirmary. He was a Fellow of the American College of Surgeons and the American Medical Association, a diplomate of the American Board of Otolaryngology, and a member of the American Academy of Ophthalmology and Otolaryngology, and the State and County Medical Societies.

PUTTI, VITTORIO: Bologna, Italy; born in Bologna, March 1, 1880; died in Rome, November 1, 1940; graduated in medicine from the University of Bologna, July 1, 1903; elected an Honorary Fellow of the Academy November 18, 1926.

Dr. Putti was professor of orthopedic surgery and dean of the School of Medicine at the University of Bologna, and director of the Rizzoli Orthopedic Institute of Bologna. He was noted for his studies on tuberculosis of the bones and was the author of numerous books on orthopedics.

ROBERTSON, VICTOR ARTHUR: 51 Eighth Avenue, Brooklyn, N. Y.; born in Brooklyn, April 19, 1861; died in Brooklyn, December 22, 1939; graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1883; elected a Fellow of the Academy March 1, 1923.

Dr. Robertson was consulting surgeon to the Coney Island Hospital, a member of the County and State Medical Societies, a Fellow of the American Medical Association and a Fellow of the American College of Surgeons.

SCHILDER, PAUL FERDINAND: 160 East 48 Street, New York City; born in Vienna, Austria, February 15, 1886; died in New York City, December 8, 1940; graduated in medicine from the University of Vienna in 1909; elected a Fellow of the Academy November 5, 1931.

Dr. Schilder was assistant psychiatrist at

the University of Halle 1909-1912, assistant psychiatrist at the University of Leipzig 1912-1914, and chief physician in the Austrian Army 1914-1918. At the University of Vienna he was assistant in psychiatry 1918-1928, assistant professor of the medical faculty 1920-1924, and professor extraordinary 1924-1929. Since 1930, he was clinical director of the Psychiatric Division of Bellevue Hospital and Associate Professor of Psychiatry at New York University College of Medicine.

Dr. Schilder was a diplomate of the American Board of Psychiatry and Neurology, a Fellow of the American Medical Association, and a member of the American Neurological Association, the American Psychiatric Association, the American Psychopathological Association, and the State and County Medical Societies.

He was the author of several books and contributed numerous articles to medical journals on neurology and psychiatry.

SCHWARTZ, JOSEPH: 1822 Grand Concourse, Bronx, New York; born in Hungary, in 1896; died in New York City, February 5, 1941; graduated in medicine from the Long Island College Hospital in 1919; elected a Fellow of the Academy January 3, 1929.

Dr. Schwartz was associate attending surgeon and associate on the laboratory staff of the Lebanon Hospital. He was a diplomate of the American Board of Urology, a Fellow of the American College of Surgeons, a Fellow of the American Medical Association, and a member of the State and County Medical Societies.

SOUTHWORTH, THOMAS SHEPARD: 530 Fifth Avenue, New York City; born in West Springfield, Massachusetts, June 7, 1861; died in New York City, November 14, 1940; received the degree of B.A. from Yale University in 1883; graduated in medicine from the College of Physicians and Surgeons in 1887; elected a Fellow of the Academy March 1, 1894.

Dr. Southworth practiced in New York City from 1887 to 1921 when he retired. He was consulting physician to the New York Nursery and Child's Hospital and the New York City Children's Hospital. He was a Fellow of the American Medical Association, a member of the American Pediatric Society and its president in 1920, and a member of the State and County Medical Societies.

WADHAMS, ROBERT PELTON: 102 East 68 Street, New York City; born in Goshen, Connecticut, January 10, 1879; died in New York City, December 16, 1940; received the degree of Ph.B. from Yale University in 1902 and graduated in medicine from New York University and Bellevue Hospital Medical College in 1906; elected a Fellow of the Academy January 15, 1920.

Dr. Wadhams was clinical professor of surgery at New York University College of Medicine, surgeon to the Bellevue Hospital, associate surgeon to the French Hospital and consultant surgeon to the St. Vincent's Hospital of New York and the Charlotte Hungerford Hospital, Torrington, Connecticut. He was a diplomate of the American Board of Surgery, a Fellow of the American College of Surgeons, a member of the American Society of Regional Anesthesia, Inc., and a member of the American Medical Association and the County and State Medical Societies.

For many years, Dr. Wadhams was a member of the Medical Corps of the New York National Guard and during the World War he served as Lieutenant-Colonel in the Medical Corps of the U. S. Army.

YUDKOWSKY, PETER: 211 Central Park West, New York City; born in Russia, March 15, 1891; died in Palm Beach, Florida, January 24, 1941; graduated in medicine from the Long Island College Hospital in 1913; elected a Fellow of the Academy January 5, 1928.

Dr. Yudkowsky was secretary of the Medical Board and attending otolaryngologist to the Sydenham Hospital and assistant surgeon to the New York Eye and Ear Infirmary. He was a diplomate of the American Board of Otolaryngology, a Fellow of the American Medical Association, and a member of the American Academy of Ophthalmology and Otolaryngology, and the County and State Medical Societies.